CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL PROFILE OF MALIGNANT SURFACE EPITHELIAL OVARIAN TUMORS

Dissertation submitted in partial fulfillment of
the requirements for the degree of

M.D. (PATHOLOGY)

BRANCH – III

INSTITUTE OF PATHOLOGY AND ELECTRON MICROSCOPY,

MADRAS MEDICAL COLLEGE,

CHENNAI – 600 003.

THE TAMIL NADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2013

CERTIFICATE

This is to certify that this Dissertation entitled **"CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL PROFILE OF MALIGNANT SURFACE EPITHELIAL OVARIAN TUMORS"** is the bonafide original work of Dr.M.KUZHAL MOZHI, in partial fulfillment of the requirement for M.D., (Branch III) in Pathology examination of the Tamilnadu Dr.M.G.R Medical University to be held in April 2013.

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I Dr.M.Kuzhalmozhi, solemnly declare that the dissertation titled **"CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL PROFILE OF MALIGNANT SURFACE EPITHELIAL OVARIAN TUMORS"** is the bonafide work done by me at Institute of Pathology, Madras Medical College under the expert guidance and supervision of Prof.Dr.M.P.Kanchana, M.D., Professor of Pathology, Institute of Obstetrics and Gynecology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of M.D., Degree (Branch III) in Pathology.

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CERTIFICATE OF APPROVAL

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Dear Dr.Kuzhalmozhi

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Clinocopathological and immunohistochemical profile of malignant surface epithelial ovarian tumors" No.17042012.

The following members of Ethics Committee were present in the meeting held on 19.04.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
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10.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL PROFILE OF MALIGNANT SURFACE EPITHELIAL OVARIAN TUMORS

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ABBREVIATIONS

HER 2 NEU	:	Human Epidermal Growth Factor Receptor 2
WHO	:	World Health Organisation
APST	:	Atypical Proliferating Serous Tumor
APMT	:	Atypical Proliferating Mucinous Tumor
TCC	:	Transitional Cell Carcinoma
PTEN	:	Phosphatase and Tensin homolog
TGF β	:	Transforming Growth Factor Beta
HNF β	:	Hepatocyte Nuclear Factor Beta
FIGO	:	International Federation of Gynecology and Obstetrics
TNM	:	Tumor, Node, Metastasis
IHC	:	Immunohistochemistry
FISH	:	Fluorescent In Situ Hybridisation
PCR	:	Polymerase Chain Reation
ELISA	:	Enzyme Linked Immune Sorbent Assay.
RR	:	Relative Risk
CI	:	Confidence Interval
N	:	Number of Cases.

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INTRODUCTION

INTRODUCTION

Ovarian tumors are the most common neoplasms in women. Among the various gynecological tumors, the pathology of ovarian neoplasms is more complex, because the ovary gives rise to various types of tumors than any other organ. The origin of ovarian tumour is often in disparity[1]. Ovarian tumours accounts for larger proportion of clinically important problems and they are usually dangerous because of their silent growth.

Worldwide, Ovarian tumor constitutes sixth most common tumor in women. Ovarian carcinoma is the fifth most common malignancy in the western countries and ranks fourth in cancer mortality[2]. In India, Ovarian cancer is the most lethal gynecologic malignancy which ranks 2nd after cervical cancer. In Chennai, ovarian cancer stands in the third position[3].

This high mortality is because of difficulty in diagnosing ovarian cancer at an early stage and absence of effective therapies for advanced stage disease [4]. PLCO screening programme is the ongoing trail designed for effective screening of ovarian cancer which includes Transvaginal USG and CA 125 level. The aim of this programme is to diagnose ovarian tumors when they are still confined to the ovaries. By this the mortality of the disease is reduced and effective cure can be obtained[5].

Ovarian carcinoma exhibits a wide range of morphological phenotypes. Since more than 90% of ovarian cancers are of epithelial cell origin, various genetic alterations occur during malignant transformation of ovarian epithelial cells. Several studies on the molecular pathways of carcinogenesis provides explanation for the different morphologic phenotypes and the prognostic behavior of ovarian carcinoma.

Genomic studies on surface epithelial ovarian tumors have proposed a new method of classification based on their gene expression patterns. Type I tumors are genetically stable and are characterized by mutations in a number of different genes including KRAS, BRAF, PTEN, and beta-catenin. Type II tumors show high level of genetic instability and is characterized by mutation of TP53[7]

Women with a family history of ovarian carcinoma or who have BRCA 1/2 mutations shows reduced risk for tumor development following prophylactic hysterectomy and bilateral salpingo-oophorectomy. Immunohistochemical markers like cytokeratin have been used in the diagnosis of ovarian tumors. Recently various studies on prognostic significance of p53, Her-2neu, overexpression in epithelial ovarian cancer suggests poor prognosis and decreased survival benefit.

More than 30% epithelial ovarian cancer shows amplification and over-expression of ERBB2 gene and they are associated with worse prognosis[8]. p53 overexpression shows an aggressive behavior and is associated with more rapid

spread of disease. Hence IHC is used to measure the Her 2 neu and p53 protein overexpression present in the epithelial tumors.

This study is undertaken in view of evaluating the incidence, age, clinical features, histopathological and immunohistochemical features of epithelial ovarian tumors and its prognostic significance. In addition, the recent literatures, journals and research publications on ovarian tumors are also reviewed.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1. To evaluate the incidence and distribution of surface epithelial ovarian carcinoma in patients admitted in Institute of Obstetrics & Gynaecology, Egmore & Institute of Social Obstetrics and Kasthurbai Gandhi Hospital, Triplicane ,Madras Medical College, Chennai during the year 2008-2012.
2. To study the histopathological features of epithelial ovarian carcinoma which includes site of involvement, tumour size, macroscopic feature, histological subtype, grade, stage, presence of ascites.
3. To study the immunohistochemical expression of P53 in epithelial ovarian carcinoma.
4. To study the immunohistochemical expression of Her2neu in epithelial ovarian carcinoma.
5. To determine the association of P53 and Her2neu expression with known clinicopathological factors such as age, stage, histological subtypes, grade and presence of ascites,

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Surface epithelial ovarian tumors is considered as a leading cause of death among all gynaecological cancers. It constitutes about two-thirds of all ovarian cancers and 90% of ovarian cancers are malignant[47]. It usually arises sporadically in 90-95% of the patients. The incidence of ovarian cancer is gradually increasing in India with crude incidence rate of 5.2.

Surface epithelial ovarian tumors are classified according to cell type as serous, mucinous, endometrioid , based on pattern of growth into cystic and solid based on amount of fibrous tissue, cellular atypia and invasiveness.

Various grading system such as FIGO, WHO, Gynecologic Oncology Group, were in use in the past, but they are not currently in place. Silverberg and colleagues[9] proposed universal grading system which includes degree of nuclear atypia, number of mitotic figures, formation of papillae and glands.

In the year 2004, Malpica Anais MD et al [10] proposed two-tier grading system for serous carcinomas which depends on the degree of nuclear atypia and number of mitotic figures. This system later compared the results with other systems of grading by Shimizu/Silverberg and the FIGO.

EPIDEMIOLOGY

A study conducted by I.Dos Santos Silva and A. J. Swerdlow [11] showed that there were increase in the incidence of ovarian tumors with significant increase in elderly age than young. It constitutes about 0.76% per year. Highest rate of incidence is seen in developed countries like Scandinavia, Israel, and North America, whereas in developing countries and in Japan incidence rate is low[12].

Bouly P et al[13] showed that incidence rate of ovarian tumors in developing countries less than 5 per lakh, but in developed countries it is less than 13 per lakh population. Risk of ovarian epithelial tumors in black women is lower than whites. Epithelial ovarian tumors are more common in developed countries because of low parity[23]

In a study conducted on the age-standardized incidence rates on ovarian cancer for the period 2001-06, highest rate of incidence were seen in Pune and Delhi. It ranges from 0.9 to 8.4 per 100,000 person years. This study also showed that the disease usually increases at the age of 35 and peaks during the age of 55-64 yrs[14]. Surface epithelial ovarian cancer is seen commonly in postmenopausal women and only 20% of the cases occur in reproductive-age group.[15]

RISK FACTORS

Villard – Mackintosh L et al [16] have suggested that women on oral contraceptives and those who show increased parity are protected from ovarian carcinoma. Early menarche and late menopause are also considered to be significant risk factors for ovarian tumors [13]. Another study suggests that ovarian cancer is more common in high socio economic group because of low fertility rates in these women.

La Vecchia C. et al[17] proved that incidence rate and mortality of ovarian tumors is less in younger individuals than the elderly. As the age increases the incidence rate also increases.

Fathalla MF et al [18]hypothesis shows that during incessant ovulation the surface epithelium of the ovary undergoes repeated trauma. As a result, the actively proliferating epithelium shows malignant transformation.

Banks E, et al[19], in their study proposed that age of first birth, feeding, weight, diet, talc, smoking habits, few childhood viral infections and irradiation are considered to be various other risk factors. Another important risk factor in ovarian cancer is genetic alterations [23] .

HISTOGENESIS OF SURFACE EPITHELIAL OVARIAN TUMORS

K M Feeley et al [20] proved by their study that Ovarian cyst usually arise from the ovarian surface epithelium which is the mesothelial lining of ovaries. Invagination of this mesothelium into the ovarian cortex stroma produces ovarian cyst. These inclusion cysts in the cortex will undergo epithelial metaplasia and progress to produce variety of surface epithelial ovarian tumors based on their differentiation[35].

S. NO	TYPES OF DIFFERENTIATION	TYPE OF TUMORS
1	Fallopian tube	Serous
2	Endocervical	Mucinous
3	Endometrial	Endometrioid
4	Mesonephric	Clear cell
5	Transitional	Brenner

Study conducted on recent concepts in origin of serous carcinoma proved that high grade serous carcinomas arise from the secretory epithelial cell of fallopian tube which is considered as a cell of origin. [21]

PATHOGENESIS

Malignant epithelial ovarian cancer such as serous carcinomas commonly arise de novo. Mucinous, endometrioid and clear cell carcinoma usually develop from its benign and atypical proliferative precursor lesions[22]. Most of the serous carcinomas with high grade differentiation disseminate extensively into peritoneum during diagnosis and present in stage II & III [23].

Yang DH et al [24], suggested that Serous carcinoma predominantly arise directly from surface epithelial inclusion cysts. It rarely develops from benign serous cystadenomas. Serous tumor usually follows rapid adenoma carcinoma sequence. Micro papillary low grade serous carcinoma mostly arises from its atypical proliferative serous tumor. Thus it is considered to follow prolonged adenoma carcinoma sequence[22]. Recent studies on the origin of ovarian cancer suggested that serous intraepithelial tubal carcinoma act as a precursor for high grade ovarian serous carcinoma [25].

Enomoto et al[26], in their study demonstrated that mucinous carcinomas commonly present as well differentiated tumor and always shows areas of benign and borderline tumor suggesting that it develops slowly from its benign counterpart in a stepwise fashion.

Prowse AH et al [27], proved that endometriosis act as a precursor lesion for both endometrioid and clear cell carcinoma. Endometriosis occurs in 7-20% of women and it is considered as a precursor for 21% of ovarian cancers [28, 22].

CLASSIFICATIONS

WHO classification of ovarian tumors is given in annexure-II.

Many classifications were proposed since 1940 for surface epithelial carcinomas. Gilks[29] suggested a classification which helps in potential biological and therapeutic implications.

1. High-grade serous, high-grade endometrioid, and undifferentiated carcinomas, and carcinosarcomas/malignant mixed müllerian tumors.
2. Low-grade serous carcinomas and serous borderline tumors.
3. Mucinous carcinomas and mucinous borderline tumors of intestinal type.
4. Low-grade endometrioid carcinomas and endometrioid borderline tumors.
5. Clear cell carcinomas.
6. Transitional cell carcinomas.

Recently Kurman et al [25] proposed a new classification which predicts the behavior of the tumor and its precursors.

Type I tumors: It is confined to the ovary during diagnosis and slow growing. It arises from borderline tumors which act as a precursor lesions. Low-grade micropapillary serous carcinoma, mucinous, endometrioid and clear cell carcinomas and malignant Brenner tumor come under this category.

Type II tumors: They grow rapidly and are highly aggressive tumors. There is no well defined precursor lesions identified. These include high-grade serous carcinoma, undifferentiated carcinoma and malignant mixed müllerian tumor.

1988, Slotman & Rao, proposed several histopathological subgroups of epithelial ovarian cancers. Now the universally accepted classification is given by WHO committee on nomenclature and terminology of ovarian tumors [30].

1. Serous tumours
2. Mucinous tumours
    - Intestinal type
    - Endocervical type

3. Endometrioid

- Adenosarcoma
- Mixed mesodermal tumour
- Endometrioid stromal sarcoma

4. Clear cell tumour

5. Transitional cell tumours (including Brenner)

6. Squamous cell tumours

7. Mixed epithelial tumours

8. Undifferentiated carcinoma

Each of these tumors is further subdivided into benign, borderline and malignant categories.

Benign tumors includes cystadenoma, papillary cystadenoma, surface papilloma , adenofibroma, cystadenofiboroma. Malignant tumors are designated as adenocarcinoma, surface papillary adenocarcinoma and cysadenocarcinoma. Intermediate groups are considered as borderline tumors or low malignant potential by WHO in 1973. At present they are called as atypically proliferating epithelial tumors [28, 30, 31].

SEROUS TUMORS

Serous tumors are the commonest neoplasm of ovary which constitutes 30% of all ovarian tumors. Of all serous tumors, benign tumors constitutes 50%, 15% are borderline and invasive carcinoma constitutes 35%.[32]. It involves 5th & 6th decades of life.

Benign serous tumors include cystadenomas, adenofibromas, and cystadenofibromas which constitute about 25% of all benign ovarian tumors[30]. 12-23% of cystadenomas are bilateral. It involves 4th and 5th decades of life. Grossly it is unilocular, thin walled cyst filled with straw coloured watery fluid with varying sizes. The inner surface is usually smooth but rarely papillary excrescences arise and protrude within lumen of cyst.

Microscopically, it is lined by a type of epithelium seen in fallopian tube [22,33] which is single layer of ciliated columnar cell. Mitosis and atypia is absent. Stroma shows edema with dense fibrovascular tissue. 15% of adenomas show psommoma bodies in the stroma. The adenofibroma will be highly cellular with abundant fibrous stroma surrounding glands and cysts.

BORDERLINE SEROUS TUMORS (APST):

It constitutes about 10% of ovarian serous tumors. It involves older age than benign tumors. It is bilateral in 35-40% of cases. Grossly, it is cystic lesion

filled by friable cauliflower like papillary excrescences without hemorrhage and necrosis.

Microscopically, APST show hierarchical type pattern of branching[22, 28]. The epithelium shows extensive stratification and tufting with detachment of cell clusters. Epithelial buds fuses to form cribriform pattern in some foci. Mild nuclear atypia and mitosis seen. There is no obvious stromal invasion. The microinvasive foci may appear as individual cells, as clusters of cells showing abundant eosinophilic cytoplasm, as confluent nests forming a cribriform pattern, as micropapillae and macropapillae[22]. Some foci also show non hierarchical branching pattern with fine micropapillae arising from the central papillae resembling micropapillary serous carcinoma.

MICRO PAPILLARY SEROUS CARCINOMA

Kurman and his group included a new category termed as micropapillary serous carcinoma which lies between the borderline and invasive carcinoma[34].

Grossly it is cystic with more papillary processes and little necrosis. Microscopically, it shows non hierarchical branching papillae which are thin with minimal fibrovascular core. Moderate nuclear atypia and increased mitosis is seen. It shows invasion in the form of solid nests or glandular structures surrounded by clear spaces[35]

SEROUS CARCINOMA

50% of the malignant ovarian neoplasms are serous carcinoma. The mean age group is 45-65 yrs. High-grade serous carcinoma is usually bilateral and spreads through ovarian surface into peritoneum requiring debulking surgery[36].

Grossly, it is large with both solid and cystic areas. Its outer surface is smooth and bosselated. Cut surface of cystic cavity show soft friable papillae filled with serous or bloody fluid. Solid areas are pink to gray and firm. An extensive area of hemorrhage and necrosis is seen.

Microscopically, the architectural pattern of the tumor varies from complex papillary to solid pattern with stratification of cells, marked nuclear atypia, mitosis, and bizarre giant cells. Stromal invasion present. Lace like or labyrinthine pattern also seen focally. Area of necrosis and hemorrhage are seen. Psommoma bodies are seen in 25% of serous carcinomas.

MUCINOUS TUMORS

Benign Mucinous cystadenoma constitutes about 76% of ovarian mucinous neoplasms. It occurs in the 3rd to 6th decades of life. They present as a pelvic or abdominal mass. Bilaterality is only 2-5%. Grossly, they are multilocular thin walled cysts with smooth surface. Cysts contain sticky mucoid material. Locules

are of varying size and largest of 50 cm and weight of 100 kg is reported so far[22]. One major cyst with many daughter cysts seen in the wall.

Microscopically, cysts are lined by 2 types of epithelium, Gastro intestinal type and Endocervical type. Intestinal type epithelium is composed of uniform tall columnar cells arranged in glandular and cystic structures with goblet cells or paneth cells. Endocervical type epithelium is associated with papillary architecture. Accumulation of mucin distends the cyst and cause leakage of mucin which is not associated with stromal reaction.

Atypical proliferative mucinous tumors constitute 12% of all mucinous neoplasms. Borderline tumors are usually unilateral. Intestinal type of borderline tumor is more common than endocervical type. Hart and Norris[37] proposed that, borderline tumor should be considered when the atypical epithelium is less than four cells in thickness and as carcinoma when it is four cells or greater.

Grossly, they are very large, multilocular cystic mass with the mucin and smooth inner lining. Many show intracystic papillary processes. Microscopically, it shows epithelial stratification with multilayering, intraluminal tufting, atypical nuclear features and mitosis. There is no stromal invasion. Endocervical type tumors show mucinous epithelium. APMT with microinvasion should not exceed 5mm diameter but multiple foci of invasion can be present.

MUCINOUS CARCINOMAS

Primary ovarian mucinous carcinomas are less common than the metastatic mucinous carcinomas. It constitutes 3.6% of ovarian epithelial neoplasia. It occur in 4^{th} to 7^{th} decade of life. Bilateral tumors are mostly metastatic while unilateral tumors are primary. Grossly, they are large multiloculated cysts measuring 15-20 cm . Inner surface shows firm fleshy white solid areas with cystic nodules. Hemorrhage and necrosis are seen.

Microscopically, glands and cysts are arranged in complex pattern with irregular infolding and protrusions. Riopel ma et al,[38] in their study suggested that the stratified epithelial lining cells which are tall picket fence cells forms multilayering exceeding three cell thickness with nuclear atypia, irregularly clumped chromatin with prominent nucleoli. Unequivocal Stromal invasion mitotic figures are prominent. Areas of necrosis seen.

Pseudomyxoma ovary is more commonly seen in mucinous tumors. There is acellular lakes of mucin entering in to ovarian stroma which is usually multifocal and extensive in two-third of the cases[39]. Cellular pseudomyxoma ovary is a condition in which pools of mucin contain clusters of epithelial cell and it is associated with poor prognosis. Pseudomyxoma peritonei is a progressive

condition in which mucin deposits with the epithelium undergo fibrous organization and get adhered to peritoneum and omentum.

ENDOMETRIOID TUMORS

According to WHO, endometriod tumors are group of tumors which show microscopic features of typical forms of endometrial neoplasia[28, 47]. Benign and borderline tumors are usually rare. Endometriod carcinomas ranks second most common ovarian carcinoma and constitute 12-30% of all malignant surface epithelium ovarian tumors.

Benign Endometrioid tumors are usually adenofibromos which is very uncommon. Bilaterality constitutes only 17%. Grossly, it is solid fibrous tumor, tan or white with small cysts resembling honeycomb appearance. Microscopically, Tubules and glands lined by endometrial type cells surrounded by fibrous stroma.

Russell and Rothe et al[40] termed borderline tumor as "proliferating endometrioid tumor". Synder et al[41] and Norris have termed them into proliferative and low malignant potential categories. Grossly, it is unilateral measuring 6 to 10 cm. They show solid areas predominantly with tan to white papillary excrescences. Microscopically, it shows increased glandular density, glandular crowding with lining epithelium showing stratification, mild nuclear atypia and mitosis. There is no stromal invasion.

ENDOMETRIOID CARCINOMA

It constitutes 10 to 20% of ovarian tumors. It involves 5^{th} to 6^{th} decades of life.13% cases are bilateral. Patients with endometrosis for long duration usually have increased tendency for ovarian carcinoma. Grossly it is a solid and cystic tumor measuring 15 – 20 cm diameter. Areas of hemorrhage and necrosis seen. Some of the cysts are filled with chocolate coloured fliud.

Microscopically, it is characterized by glandular, papillary, villoglandular and cribriform pattern .There is infiltration of stroma by confluent growth. Degree of atypia, stratification and solid growth pattern increases as the grade increases. 20-50% of endometrioid carcinoma shows areas of squamous differentiation.[28]

CLEAR CELL TUMORS

It is less common epithelial tumor which constitute 5 -10 % of ovarian carcinoma. Schiller in 1939[42], coined the name ‘ mesonephroma’ for tumors which had hobnail cells and glomeruloid bodies. Teilum called these glomeruloid bodies as Schiller-Dual bodies and recognized it to be seen in Yolk sac tumors. Scully and Barlow[43] suggested that clear cell tumors arise from endometriosis.

Clear cell adenofibroma is very rare. Occurs in 5-6th decades. Bilaterality is less than 10%. Grossly, it has smooth outer surface with cystic and solid cut surface. Microscopicaly, tubular glands lined by hobnail cells with minimal nuclear atypia and mitosis. The stroma shows fibrocollagenous tissue. Atypical proliferating clear cell tumor grossly appears similar to adenofibroma with soft and fleshy areas. Microscopically, it shows marked epithelial proliferation and atypia with no stromal invasion.

Clear cell carcinoma constitutes only 2.4% of ovarian epithelial tumors. 30-35% of clear cell carcinomas show association of endometriosis. Grossly, it is a large tumor measuring 10-30cm dia. Inner surface shows thick walled cyst filled with fleshy nodules projecting in to lumen.

Montag A.G et al[44] analysed 44 cases of clear cell ca and described 3 types of cells- clear cells, cells having eosinophilic granular cytoplasm and hobnail cells which are arranged in tubular, glandular and papillary pattern. Hobnail cells are columnar with clear to eosinophilic cytoplasm with apical nuclei that bulge into lumen. PAS positive eosinophilic hyaline globules are seen around the malignant cells. A predominant tubulocystic architectural pattern has good prognosis, but the cell type has no significant difference in survival.

BRENNER TUMOR

It constitutes 2-3% of all ovarian tumors. Benign tumors are more common than the malignant tumors. Grossly, it is circumscribed, firm, gray white solid tumor with foci of calcification. Microscopically, nests and cords of polygonal epithelial cells which resemble urothelial cells grows in a fibrous stroma. Nuclear groove is characteristic feature of Brenner tumor. Atypia and mitosis is absent. Stroma will be densely fibrous. Dystrophic calcification is seen in the hyalinised areas. Most of the tumors will be associated with mucinous tumors[47].

Borderline brenner tumor is circumscribed grey white to tan solid with partially cystic cavity showing papillae projecting into lumen. Microscopically, the intracystic papillae will be lined by transitional type of epithelium which resembles low grade non invasive papillary transitional cell carcinoma of urinary tract. No stromal invasion is seen.

Roth L M et al[45]in their study on ovarian Brenner tumor have classified them as Proliferative transitional cell tumors if its epithelium is similar to grade 1 and 2 of urothelial papillary TCC and low malignant potential tumor, if it is similar to grade 3 of urothelial papillary TCC.

Malignant brenner carcinoma occurs in 50-70 years of age. Grossly, it is unilateral showing solid and partly cystic areas with foci of calcification.

Hemorrhage and necrosis also seen. Microscopically, it shows features similar to high grade transitional cell carcinoma of urinary tract. Cells are polygonal with amphophilic cytoplasm and pleomorphic atypical nuclei with increased mitotic figures. Confluent masses or irregular cords of cells invade stroma. Benign or atypical Brenner components should be present for diagnosis of malignant Brenner tumor[46].

UNDIFFERENTIATED CARCINOMA

It consists of 5% ovarian cancer. It is poorly differentiated and associated with worse prognosis. It is usually bilateral. Grossly, it is large solid tumor with hemorrhage and necrosis. Microscopically, it is composed pleomorphic epithelial cells with variable amount of cytoplasm, vesicular nuclei with prominent nucleoli. Abnormal mitosis and bizarre tumor giant cells seen.

MOLECULAR PATHOLOGY

Cytogenetic study on ovarian tumors identified loss of chromosomes X, 22, 18, 17, gain of chromosomes 12, 8 and rearrangements of 1, 3, 6, 19 chromosomes. There is also amplication of HER2NEU, cyclin D1, cyclin A, P21 oncogenes. Serous carcinomas shows positive staining for WT1 and PAX8 genes [47] .

Women with BRAF 1& 2 mutated gene have increased risk to develop type 1 group of ovarian cancer. 60% of the high grade ovarian serous carcinoma shows P53 gene mutation[48]. KRAS mutation is more common in mucinous ovarian tumor. Dysregulation of the WNT signaling pathway, Micro satellite instability and Beta catenin mutation is seen in 40% of of endometrioid tumors. PTEN inactivation is seen in 20% endometriod carcinoma [25]. Over-expression of HNF-1beta and TGF beta 2 leads to Clear-cell carcinomas. The genetic alterations in transitional-cell carcinomas of ovary remain unknown[49].

IMMUNO HISTOCHEMICAL PROFILE

In 1941, Albert Coons et al first introduced direct labeling of antibodies with fluorescent isocyanate. Nakane and Pierce et al in 1966, then started indirect labeling technique in which unlabelled antibody is followed by second antibody or substrate. Various methods of Immunohistochemistry includes peroxidase – antiperoxidase method (1970), alkaline phosphatase labeling (1971), avidin biotin method (1977) and two layer dextrin polymer technique (1993).[50]

Serous carcinomas will be CK7 positive and CK 20 negative. It is also positive for EMA, CAM 5.2, B 72.3, AE1/ AE3, CA 125 in 85% of cases. Mucinous carcinoma are usually CK 7 positive, they also stain for CDX-2. CK 20 staining is variable in mucinous carcinomas. Endometrioid carcinomas will be

positive for CK 7 and CK 20. WT-I is negative which helps to differentiate it from endometrial carcinomas. Clear cell carcinoma show positive for CK7, 34BE12 , Leu M1, B72.3 and CA 125[51,22,,28.47]

TUMOR SPREAD AND STAGING

Ovarian cancer spreads beyond pelvis extensively during diagnosis in 70 to 75% of patients[7]. Local extensions, lymphatic and intra abdominal dissemination are the common mode of spread. Most common sites include contralateral ovary, peritoneal cavity, para-arotic and pelvic lymphnodes, lung and liver. Umbilical metastasis sometimes may be the first manifestation termed as Sister Joseph nodule. Borderline tumors have a tendency for both invasive and non invasive peritoneal implants [47].

FIGO staging is the most powerful predictor of prognosis[32, 28]. TNM systems are based on post operative pathological staging. FIGO Staging is given in annexure III.

PROGNOSIS

The overall prognosis of ovarian carcinoma remains poor due to its rapid growth and absence of early symptoms. Hence majority of the patients present in advanced stage during diagnosis. The survival rate is 35% at 5 yrs, 28% at 10yrs and only 15% at 25 yrs.

Chan J.K et al[52] proposed various factors like age, FIGO staging, tumor histological type, grade, ascites, fluid cytology, CA125 level, presence of residual disease which all have influence on the prognosis of ovarian tumors.

In 2008, Oldenhuis et al[53], suggested that molecular biological factors also predicts the prognosis and have therapeutics values. P53, Her2neu over expression and BRCA1 mutation affect the survival of the patients.

Patients of age older than 60yrs and advanced stage were associated with poor prognosis[54]. Patients with stage 1 disease have better survival of 90%. Patients with stage IV have poor prognosis and survival is only 10-20% because of wide spread metastatic disease. Lee-jones L[12] analysed epithelial tumors and demonstrated the 5 yr survival rate in various stages of disease. In Stage -I disease survival rate is 82% and in Stage-II reduces to 64%, Stage III – 38%, in stage IV it is only 14%. Younger patients have better prognosis. This is because they present at early stage and disease is lower grade in these young women[55]. Positive peritoneal cytology usually indicates the presence of extra ovarian disease. Serous and endometrioid carcinomas are more often show positive for ascitic fluid cytology. High grade ovarian tumors are more positive than low-grade tumors.[56]

Tumor grade also affects the prognosis. As already described, Silverburg and colleagues[9] proposed universal grading system which pointed out that grading also helps in predicting response of the tumor to chemotherapy. Serous Carcinomas have worst prognosis. Micro papillary serous tumor shows increased recurrence of invasive carcinoma and tumor deaths. Mucinous carcinomas have excellent prognosis. The prognosis of endometrioid carcinoma is better than the serous or mucinous carcinoma. Clear cell carcinoma have poor prognosis and they always show resistant to chemotherapy[44].

Austin and Norris[46] pointed out that the prognosis of malignant Brenner tumors with an associated benign component is better than transitional cell carcinomas (non-Brenner type). Tumors showing aneuploidy generally present as high grade and they behave more aggressively than the diploid tumors. CA-125 serum markers are more useful in the initial evaluation of these patients and in the follow-up to diagnose the recurrent disease. Thus it is considered to be an independent prognostic factor. Overexpression of P53 and HER2NEU has been suggested to be a marker of poor prognosis in most of the studies[47, 53].

HER 2 NEU

HER2 neu (Human Epidermal growth factor Receptor 2) also known as cerbB2 is an oncogene belongs to EGFR family[57]. It encodes a 185 kDa transmembrane glycoprotein with tyrosine kinase activity.

The proto-oncogene is encoded in the long arm of chromosome 17(17q11.2 – 12) gene [22, 57]. HER-2/neu gene contains a cysteine rich extracellular ligand binding domain, a hydrophobic

membrane spanning region, and an intracellular tyrosine kinase domain. These domains activates multiple signaling pathways like mitogen activated Protein kinase, Phospholipase C, signal transducer and activator of transcription (STAT) signaling through ERBB family of receptors thereby regulating cell proliferation , differentiation and inhibits apoptosis.

Padhy L.C et al[58] in 1982 identified this oncogene which was associated with the development of neuroblastomas in rats exposed to ethylnitrosourea in utero due to point mutation on the membrane spanning region. In humans, only HER-2/neu amplification and overexpression rather than point mutation produces malignant tumors[54, 58].

Several studies on breast carcinomas have suggested that overexpression of Her2neu occurs in 15-40% of cancers and is associated with poor survival[58].

Amplification and overexpression is also seen in other human malignancies including ovarian cancer, stomach and uterine cancer. Her 2 neu positivity in endometrial carcinomas indicates aggressive behavior due to its extensive metastasis. The prognostic significance of Her2neu overexpresion in surface epithelial tumors remains controversial.[59,60,61,62,]

Her2neu is negative in normal ovary. Ovarian carcinoma shows Her2neu positivity in one third of cases. Amplification and over- expression of ERBB2 gene occurs in 30% of ovarian cancer[8]. It is associated with increased disease recurrence and worse prognosis. Her2neu protein overexpression is studied by IHC and gene amplification by FISH.

FISH is used as secondary test in equivocal 2+ IHC categories to clarify HER2 status of these cases. Other methods of HER 2 testing techniques include Chromogenic Insitu Hybridization, PCR, ELISA and Southern blotting.

Trastuzumab is a humanized monoclonal antibody that acts by targeting the HER2 extracellular domain and thereby inhibits proliferation of Her2neu positive tumor cell. The extracellular domain of HER 2 is shed from the surface of tumor cells and enters the circulation. Hence measurement of this serum Her2 is also used in predicting response to herceptin therapy. Nec vax is a newly identified

Peptide based immunotherapy that directs ‘ killer’ T cell to target and destroy neoplastic cells expressing HER 2 which is under trial.

Her 2 neu in ovarian tumors is studied not only as prognostic marker but also for herceptin treatment. Her 2 neu overexpression is associated with more aggressive behavior and with poor survival[58,8]. Some study shows that it has no prognostic significance. Further studies on Her 2 overexpression also show that it is associated with chemotherapy resistance[22]. Hence this study is done to analyze the overexpression of Her 2 neu in ovarian carcinoma and its association with more aggressive behavior and poor survival.

P53

P53 is a tumor suppressor protein which encodes T P53 gene and is located in short arm of Ch – 17 (17 p 13.1)[62]. This gene encodes 53 kDa phosphoprotein which act as a transcription factor. It regulates cell cycle and function as a tumor suppressor gene by preventing cancer. Hence P53 is also known as “the guardian of genome”[63]. It plays a role in apoptosis, genomic stability and inhibits angiogenesis. It induces growth arrest and activates DNA repair proteins when it is damaged.[64]

P53 down regulate cell cycle and act as cell cycle checkpoints. P53 is a transcription factor which on DNA damage is activated and induces transcription

of P21, a cyclin dependent kinase inhibitor to arrests DNA synthesis and thus cause cell cycle arrest. Certain mutagens such as chemical, radiation, viruses cause damage to p53 gene. Loss of functional p53 leads to variety of malignancies due to inability of cells to undergo apoptosis and show resistance to chemotherapy.

Mutation of p53 gene is the most common molecular genetics change associated with various cancers including ovarian cancers. Inherited T P53 gene mutation cause Li- fraumeni syndrome. P53 inactivation also leads to cervical cancer. P53 overexpression is associated with poor prognosis in breast cancer, lung and colorectal carcinomas.[65.66,67.] P53 gene mutation and overexpression is seen in 50 to 60% of ovarian cancer[68]. Studies on Atypical proliferating serous and mucinous tumor also suggested that it shows P53 mutation. Mutation in P53 usually occurs in DNA binding domain.

Immunohistochemical assay is done to detect overexpression of p53 protein. 50% of ovarian carcinomas shows staining for p53 with strong positive nuclear staining is seen in 30% to 50% of serous carcinomas. Benign and borderline serous tumors are usually p53-negative.

Studies by the Gynecologic Oncology Group have shown that overexpression of p53 is due to missense mutation and it is associated with poor prognosis in advanced ovarian cancers[69]. Advanced stage disease shows increased frequency of overexpression of about 40% to 60% than the stage I disease which is only 10% to 20%. This higher frequency of p53 overexpression in advanced stage patients indicates that it is a late event in ovarian carcinogenesis.

Eltabbakh GH, et al have shown that p53 plays a major role in inducing apoptosis following chemotherapy-induced DNA damage. Some in vitro ovarian cancer studies have demonstrated that loss of p53 is responsible for chemoresistance[70]. Further studies on this functionally inactive p53 also show that it behaves aggressively due to inability to repair mutated genes. Additional studies are under study to define the roles of p53 in regulating therapeutic responsiveness and patient outcome.

Sheridan E et al[71] in their study on P53 mutation and prognostic significance have shown that P53 overexpression is seen in tumors with increasing stage and grade suggesting that it has poor prognosis.

Reles et al[72], suggested controversial thought that neither P53 mutation nor expression in ovarian cancer was associated with poor survival of the patients

Various commonly used methods to detect the alteration in P53 gene are IHC, PCR-SSCP, Flow Cytometry and genomic sequencing. In IHC, brown staining of the nuclei is considered as positive.

In this study, P53 overexpression detected by IHC on surface epithelial ovarian tumors and its prognostic significance is analysed.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study is a retrospective descriptive study of malignant surface epithelial ovarian tumors conducted in the Madras Medical College- Institute of Obstetrics & Gynaecology, Egmore & Institute of Social Obstetrics and Kasthurbai Gandhi Hospital, Triplicane during the period between Jan 2008 and Oct 2012.

SOURCE OF DATA

All cases of malignant surface epithelial ovarian tumors reported in hysterectomy and salphingo ophorectomy specimen received in the Institute of Obstetrics & Gynaecology, Egmore & Institute of Social Obstetrics and Kasthurbai Gandhi Hospital, Triplicane between Jan 2008 to Oct 2012. A total of 850 ovarian tumor specimens were received during this period. Out of these, 162 cases were malignant surface epithelial ovarian tumors.

INCLUSION CRITERIA

All Malignant Surface Epithelial Ovarian Tumors reported in the study period.

EXCLUSION CRITERIA

- Non neoplastic lesions and benign tumors of ovary.
- Other ovarian tumors with surface epithelial components.

METHOD OF DATA COLLECTION

Detailed history of the cases regarding age, site of the tumor, type of procedure, history of neo adjuvant therapy, details of gross characteristics such as tumor size, soild, cystic papillary areas, CA125 Level were obtained for all the 162 cases reported during the period from Surgical Pathology records. Freshly cut and Hematoxylin Eosin stained 4 µ thick sections of the paraffin tissue blocks of specimens were reviewed and their histological subtypes (serous, mucinous, endometrioid, clearcell, Brenner) and grade (well, moderate, poorly differentiated) and stage were studied. They are further evaluated for the presence of ascites, involment of omentum by tumor cells. 50 cases of all subtypes and grade from surface epithelial ovarian carcinoma were randomly selected from the total cases and their representative formalin fixed paraffin embedded tissue samples with sufficient tumor available were subjected to IHC for a panel of 2 markers. The results were recorded with photographs. Follow up data of these patients regarding the adjuvant therapy, dose, duration, recurrence, survival data were obtained from Medical Records Section of Department of Oncology.

IMMUNOHISTOCHEMICAL EVALUATION

Immuohistochemical analysis of a 2 markers , Human epidermal growth factor receptor 2 (Her 2 neu) and P 53 were done in paraffin embedded tissue samples

Using supersentive polymer HRP system based on non biotin polymeric technology.

4 µ thick sections from selected formalin fixed paraffin embedded tissue samples were transferred onto gelatin coated slides. Heat induced antigen retrieval was done. The antigen is bound with rabbit monoclonal antibody against Her2neu protein and mouse monoclonal antibody against p53 protein and then detected by the addition of secondary antibody conjugated with horse radish peroxidase-polymer and Diaminobenzidinesubstrate. The step by step procedure of Immunohistochemistry is given in Annexure IV.

ANTIGEN	VENDOR	SPECIES	DILUTION	POSITIVE CONTROL
Her 2 neu	BIOGENEX	Rabbit	Ready to use	Breast cancer
P53	BIOGENEX	Mouse	Ready to use	Breast cancer

INTERPRETATION & SCORING SYSTEM

The immunohistochemically stained slides were analyzed for the presence of reaction, cellular localization (nuclear/cytoplasmic/membranous/combinations), percentage of cells stained and intensity of reaction. Nuclear staining was assessed for P53 and membranous staining for Her2neu. P53 was scored based on percentage of tumor cells showing positive nuclear staining. >10% of tumor cells

showing immunonuclear staining were considered as positive. Positive staining in less than 10% of cells were taken as negative. Ellis and Wolff recommendations[73] were used to assess Her2 neu positivity. An estimation of more than 10 % of tumor cells with cytoplasmic staining was considered as positive reaction for Her 2 neu. In this study, Her 2 neu score of 0 and 1+ were considered as negative and score 2+ equivocal and 3+ were considered as positive.

STATISTICAL ANALYSIS

The statistical analysis is performed using statistical package for social science software version 11.5. Correlation between Her2neu and P53 overexpression and clinicopathological prognostic factors such as age, tumor size, CA 125 level, subtypes, grade, and stage in these patients was analyzed using Pearson chi square test. P53 and Her 2 neu results were studied as positive or negative for the purpose of statistical analysis.

SURVIVAL ANALYSIS

All the patients who underwent surgery were given chemotherapy. 6 courses of cisplatin and cyclophosphamide every 21 days were given. Then the patients were followed up until the period of study. Survival data were collected from the date of initiation of treatment until death from any cause. Median follow up of 15 months were done. Surviving patient's data were calculated at the date of last visit.

Disease progression was estimated from the date of treatment initiation until the date of progression or death without documented relapse. Results were interpreted as those survived and not survived for the purpose of statistical analysis. Relative risk (RR) and their 95% confidence interval were calculated. Only p values less than 0.05 was reported as significant.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

In the study period of 5 yrs from 2008 to 2012, a total of 850 ovarian specimens were received in the Institute of Pathology, Madras Medical College Institute of Obstetrics & Gynaecology, Egmore & Institute of Social Obstetrics and Kasthurbai Gandhi Hospital, Triplicane for histological examination. Of these surface epithelial ovarian cancer accounted for 638 cases with a percentage of 75.1. The total number of benign, borderline, malignant cases was 441, 35 and 162 respectively. Thus the distribution of benign tumors was 69.1%, borderline tumors 5.5 % and malignant tumors were 25.4 % among the surface epithelial ovarian cancer specimens. Serous carcinoma constitutes 55.6%, mucinous 17.9%, endometrioid 21%, clear cell 3.7% and mixed tumors constitutes 1.9% of all malignant surface epithelial ovarian tumors.

Ovarian cancers had a peak incidence in the age group of 41-50 years. The Youngest age of presentation of ovarian cancer was 21 years in this study, with mean age of 47 yrs.

Among the 162 cases, 68 cases(42%) were reported in age of 41-50yrs and 48 cases(29.6%) were reported in age of 51-60 yrs. Only 4.9% of the cases presented in the 2^{nd} to 3^{rd} decades of life. (Table 1)

TABLE 1: AGE WISE DISTRIBUTION OF EPITHELIAL OVARIAN CANCERS

AGE	FREQUENCY	PERCENTAGE	MEAN
21-30	8	4.9	47.7
31-40	28	17.3	
41-50	68	42.0	
51-60	48	29.6	
61-70	10	6.2	
TOTAL	162	100.0	

Among the 162 cases, 71 cases (43.8%) presented with right ovarian mass, 48 cases (29.6%) had left ovarian mass and 43 cases (26.5%) had bilateral ovarian mass. (Table 2 and Chart 1)

TABLE 2: DISTRIBUTION OF SITE OF INVOLVEMENT IN OVARIAN CARCINOMA

SITE	FREQUENCY	PERCENTAGE.
Left	71	43.8
Right	48	29.6
Bilateral	43	26.5
Total	162	100.0

62 cases (68.89%) of the serous carcinomas, 25 cases (86.2 %) of mucinous carcinomas and 25 cases (73.5%) of endometrioid carcinomas were unilateral at the time of presentation . 83.3% of Clear cell carcinoma presented as unilateral tumor. Bilaterality in serous and mixed tumours was 28 cases (31.11%) and one case (33.33%) respectively. In mucinous carcinoma only 13% of cases were bilateral. (Table-3)

TABLE 3: DISTRIBUTION OF SITE BASED ON HISTOLOGICAL TYPES

TUMORS	UNILATERAL		BILATERAL	
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE
Serous	62	68.89	28	31.11
Mucinous	25	86.2	4	13.8
Endometrioid	25	73.5	9	26.5
Clearcell	5	83.33	1	16.67
Mixed	2	66.67	1	33.33
Total	119	75.71	43	24.29

Epithelial carcinoma can be grouped into following types according to their gross morphology. Among the 162 cases, 48(29.6%) of cases were both solid and cystic, 35(21.6) of cases were purely solid tumors. 30 cases (18.5%) presented with papillary excrescence in solid tumors. 18 cases (11.1%) showed multiloculated cyst. 7cases (4.3%) were purely cystic. 10 cases of cystic and 14 cases of solid and cystic tumors also presented with papillary excrescence. (Table 4 and Chart 2)

TABLE 4: DISTRIBUTION OF OVARIAN CARCINOMA BASED ON GROSS MORPHOLOGY

GROSS	FREQUENCY	PERCENTAGE
Solid/ Cystic	48	29.6
Solid	35	21.6
Solid, Papillary	30	18.5
Multiloculated cystic	18	11.1
Solid/ Cystic, Papillary	14	8.6
Cystic, Papillary	10	6.2
Cystic	7	4.3
Total	162	100.0

Ovarian tumor distribution according to their histological subtypes is shown in the Table-5. 55.6% of serous carcinoma, 7.9% of mucinous, 21% of

endometrioid, 3.7% of clear cell type and 1.9% of mixed type tumor was observed. (Table 5 and Chart 3)

TABLE 5: DISTRIBUTIONS OF HISTOLOGICAL SUBTYPES OF OVARIAN CANCERS

HISTOLOGICAL TYPE	FREQUENCY	PERCENTAGE
Serous	90	55.6
Endometrioid	34	21.0
Mucinous	29	17.9
Clear cell	6	3.7
Mixed tumors	3	1.9
Total	162	100.0

83.3% of the tumor with solid papillary excrescences was reported as serous carcinomas. 78.6 % of the tumor showing solid cystic papillary excrescences belonged to serous carcinoma. 77.8% of the tumors with multiloculated cyst were reported as mucinous carcinomas. 57% of the purely cystic tumor was mucinous carcinomas. 34% of the purely solid tumors belonged to endometrioid carcinomas. Clear cell carcinoma showed varying gross morphology as shown in the Table 6.

TABLE 6: DISTRIBUTION OF HISTOLOGICAL SUBTYPES BASED ON THEIR GROSS MORPHOLOGY

GROSS MORPHOLOGY	SEROUS N (%)	MUCINOUS N (%)	ENDOMETRIOID N(%)	CLEAR CELL N (%)	MIXED N (%)
Solid with papillary	25 (83.3)	1(3.3)	2(6.7)	2 (6.7)	-
Solid cystic with papillary	11 (78.60)	1(7.1)	2(14.3)	-	-
Pure solid	20 (57.1)	-	12(34.3)	2(5.7)	1(2.9)
Cystic with papillary	5 (50)	2(20)	3(30)		
Solid with cystic	23 (47.9)	7(14.6)	15(31.3)	2 (4.2)	1(2.1)
Pure cystic	2 (28.6)	4 (57.1)	-	-	1(14.3)
Multiloculated cystic	4 (22.2)	14 (77.8)	-	-	-

Among the study sample, 85 cases of carcinomas were less than 10cm, 67 cases had size between 10-20 cm, and 10 cases showed tumor size of more than 20cm. The size of the tumor ranges from 5 cm to 34 cm. The mean size of the tumor is 10cm. (Table 7)

TABLE 7: DISTRIBUTION OF SIZE IN OVARIAN CARCINOMA

SIZE	NO OF CASES	FREQUENCY	MEAN
<10 cm	85	52.5	10.99
10-20 cm	67	41.4	
>20 cm	10	6.1	

Among the 85 cases with size less than 10cm, 60 cases (70.6%) were serous type. Out of 10 cases with size more than 20 cm, 6 cases (60%) were mucinous carcinomas. Other carcinomas were in size between 11-20 cm. (Table 8)

TABLE 8: DISTRIBUTION OF SIZE BASED ON HISTOLOGICAL SUBTYPES

	< 10 cm N (%)	**11-20 cm N (%)**	**>20 cm N (%)**
Seruous	60(70.6)	27 (40.3)	3(30)
Mucinous	3 (3.5)	20(29.9)	6(60)
Endometriod	15(17.7)	18(26.9)	1(10)
Clearcell	5(5.9)	1(1.5)	-
Mixed	2(2.4)	1(1.5)	-
Total	85(100%)	67(100%)	10(100%)

Ovarian carcinomas were graded according to Silverberg's grading system. In this study 70 cases (43.2) were in grade-I, 48 cases (29.6%) were in grade II and 44 cases (27.2%) were in grade III. (Table 9 and Chart 4)

TABLE 9: DISTRIBUTION OF GRADE IN OVARIAN CARCINOMAS

GRADE	**FREQUENCY**	**PERCENTAGE**
I	70	43.2
II	48	29.6
III	44	27.2
Total	162	100.0

Out of 90 cases serous carcinomas, 34cases (37.7%) were in grade II, 28 cases were in grade I and III. Among the 29 mucinous carcinomas, 25 cases (86.2%) were in grade I differentiation. 50% of endometrioid carcinomas were presented as grade I tumors. All 6 cases of clear cell carcinoma (100%) were in grade III. (Table 10)

TABLE 10: DISTRIBUTION OF GRADE BASED ON HISTOLOGICAL TYPES

TUMORS	GRADE-1	GRADE-II	GRADE-III
Serous n= (90)	28 (31.11%)	34 (37.77%)	28 (31.11%)
Mucinous n=(29)	25 (86.2%)	2 (6.9%)	2 (6.9%)
Endometrioid n=(34)	17 (50%)	11 (32.35%)	6 (17.65%)
Clear cell n=(6)	-	-	6 (100%)
Mixed n=(3)	-	1 (33.33%)	2 (66.67%)
Total	70	48	44

Among the study sample, 70 cases (43.2%) presented in early stage (stage I & II) and 92 cases (56.8%) presented in late stage (III&IV). (Table 11 and Chart 5)

TABLE 11: DISTRIBUTION OF STAGE IN OVARIAN CARCINOMA

STAGE	FREQUENCY	PERCENTAGE
Late (Stage III & IV)	92	56.8
Early (Stage I &II)	70	43.2
Total	162	100.0

Among the various histological types, 63cases (70%) serous carcinomas were observed in late stage, 66.7% of clear cell carcinoma in late stage. Increased frequency of cases in early stage was observed in 62.1% of mucinous and 64.7% of endometrioid carcinomas. (Table 12)

TABLE 12: DISTRIBUTION OF STAGE WITH HISTOLOGICAL TYPES

	SEROUS	MUCINOUS	ENDOMETRIOID	CLEAR CELL	MIXED
Late	63(70%)	11(37.9)	12(35.3)	4(66.7)	2(66.7)
Early	27(30%)	18(62.1)	22(64.7)	2(33.3)	1(33.3)
Total	90(100%)	29(100%)	34(100%)	6(100%)	3(100%)

In this study, 126 cases (77.8%) showed the presence of ascites and 36 cases (22.2%) did not have ascites.(Table 13)

TABLE 13: DISTRIBUTION OF OVARIAN CARCINOMA BASED ON PRESENCE OF ASCITES

ASCITES	FREQUENCY	PERCENTAGE
Present	126	77.8
Absent	36	22.2
Total	162	100.0

6 cases (100%) of clear cell carcinomas and mixed carcinomas showed the presence of ascites followed by 77cases (85.5%) of serous carcinomas. Patients with other histological subtypes also had ascites (61-65%). (Table 14)

TABLE-14:DISTRIBUTION OF PRESENCE OF ASCITES WITH HISTOLOGICAL SUBTYPE.

TUMOR TYPE(N)	PRESENCE OF ASCITES	PERCENTAGE
Clear cell ca(6)	6	100
Mixed type(3)	3	100
Serous(90)	77	85.5
Mucinous(29)	19	65.51
Endometrioid(34)	21	61.76
TOTAL	126	77.8

Among the 162 cases, 80 cases (49.4%) showed omentum deposits and 82 cases (50.6%) do not show omental deposits. (Table 15)

TABLE 15: DISTRIBUTION BASED ON OMENTUM INVOLVEMENT

OMENTUM	FREQUENCY	PERCENTAGE
Negative	82	50.6
Positive	80	49.4
Total	162	100.0

In the present study, 55 cases (61.1%) of serous carcinoma had omentum deposits, 10 cases of mucinous (34.5%) and 10 cases of endometrioid (29.4%) carcinoma showed carcinomatous deposits. Out of 6 cases of clear cell carcinoma 4 cases (66.6%) had omentum deposits. (Table 16)

TABLE 16: DISTRIBUTION OF OMENTUM INVOLVEMENT WITH HISTOLOGICAL TYPE

SUBTYPES	FREQUENCY	PERCENTAGE
Clearcell	4	66.7
Serous	55	61.1
Mucinous	10	34.5
Mixed	1	33.3
Endometriod	10	29.4

RESULTS OF IMMUNOHISTOCHEMICAL STUDIES

Of the total 162 cases, 50 cases of varying types, grade and stage were selected in a random manner and subjected to immunohistochemical analysis with a panel of 2 markers – P53 and Her2neu. Prognosis and survival data were

analyzed on these 50 patients. The age of the patients ranged between 26 and 70 with a mean of 49 yrs. There were 9 cases (18%) below 40 years of age and

cases (82%) more than 40 years. 15 cases (30%) were located in left ovary, 23 cases (46%) in right ovary and 12 cases (24%) were bil'[ateral tumor. Grossly, 18 cases (36%) showed both solid and cystic areas, 15 cases (30%) solid with papillary excrescences, 6cases (12%) purely solid, 6cases (12%) with solid cystic with papillary excrescences and 4 cases (8%) presented as multiloculated cyst. The tumor ranged in size from 5 cm to 34cm with the median size of 10cm. There were 28cases(56%) with tumor size less than 10cm, 14cases (28%) with tumor size between 10 to 20cm and 8 cases(16%) were in size more than 20cm. Histologically, 29 cases (58%) belonged to serous type, 12 cases(24%) belonged to endometrioid, 6 cases(12%) were mucinous, and 3 cases(6%) belonged to clear cell type. 21 cases(42%) were well differentiated carcinomas, 13 cases (26%) showed moderate differentiation and 16 cases(32%) were poorly differentiated carcinomas. 33 cases(66%) belonged to advanced stage, 17cases(34%) were in early stage. In this sudy group, 38 cases (76%) had ascites and 12 cases (24%) did not have ascites. Omental involvement was seen in 30 cases (60%) of patients and it was absent in 20 cases (40%).

TABLE 17: DISTRIBUTION OF OVARIAN CARCINOMA AMONG THE VARIOUS CLINICOPATHOLOGICAL GROUPS FOR THE IHC STUDY (50 CASES)

CLINICOPATHOLOGICAL FACTOR		**NO OF CASES**
AGE	>40 yrs	39(78%)
	<40 yrs	11(22%)
SITE	Right	23(46%)
	Left	15(30)
	Bilateral	12(24)
GROSS	Solid/ Cystic	18(36%)
	Solid, papillary	15(30%)
	Solid	6(12%)
	Solid/ Cystic, papillary	6(12%)
	Multiloculated	4(8%)
	Cystic, papillary	1(2%)
SIZE	<10 cm	28(56%)
	10-20 cm	14(28%)
	>20 cm	8(16%)
STAGE	Late	33(66%)
	Early	17(34%)
GRADE	G-I	21(42%)
	G-II	13(26%)
	G-III	16(32%)
TYPE	Papillary serous ca	29(58%)
	Endometrioid ca	12(24%)
	Mucinous ca	6(12%)
	Clear cell carcinoma	3(6%)
ASCITES	Present	38(76%)
	Absent	12(24%)
OMENTAL DEPOSITS	Present	30(60%)
	Absent	20(40%)

In this study, out of 50 cases, 24 cases (48%) expressed positivity to P53 and 26 cases (52%) were negative for P53.Only 2 cases (4%) expressed positive to Her 2 neu (3+) and 48 cases(96%) were negative for Her 2 neu expression.(Table 18)

TABLE 18: DISTRIBUTION OF P53 EXPRESSION AND HER 2 NEU IN OVARIAN CARCINOMA

IHC	**P53**		**HER2NEU**	
RESULTS	POS	NEG	POS	NEG
	24(48%)	26(52%)	2(4%)	48(96%)
TOTAL	50(100%)		50(100%)	

CORRELATION OF P53 WITH VARIOUS CLINICO- PATHOLOGICAL FACTORS

P53 positivity was noted in 45.5% patients with age less than 40 and in 48.7% patients with age more than 40yrs. The mean age of patient expressed P53 positivity was 49 yrs. (Table 19)

TABLE 19: CORRELATION OF AGE WITH P53 EXPRESSION

P53	**AGE**		**N**	**MEAN**	**STD. DEVIATION**	**P-VALUE**
	<40yrs	>40yrs				
Positive	5	19	24	49.13	9.799	0.351
Negative	6	20	26	46.58	9.347	

In this study, P53 positivity was observed in 50% of bilateral ovarian carcinomas, 66.7% of patients of left ovary and 34.8% of patients of right ovarian carcinoma. (Table 20)

TABLE 20: CORRELATION OF TUMOUR SITE WITH P53 EXPRESSION

VARIABLES		P53				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
SITE	Left	10	66.7	5	33.3	15	100.0	0.157
	Right	8	34.8	15	65.2	23	100.0	
	Bilateral	6	50.0	6	50.0	12	100.0	
	Total	24	48.0	26	52.0	50	100.0	

Among the various gross types, P53 positivity is seen in 66.7% of tumor with solid & papillary excrescences, 38.9% of solid and cystic, 33.3% of solid cystic with papillary excrescences, 25% of multiloculated cystic and 100% of cystic papillary morphology. (Table 21)

TABLE 21: CORRELATION OF GROSS MORPHOLOGY WITH P53 POSITIVITY

VARIABLES		P53				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
GROSS	Solid/ Cystic	7	38.9	11	61.1	18	100.0	0.430
	Solid, papillary	10	66.7	5	33.3	15	100.0	
	Solid/ Cystic, papillary	2	33.3	4	66.7	6	100.0	
	Solid	3	50.0	3	50.0	6	100.0	
	Multiloculated	1	25.0	3	75.0	4	100.0	
	Cystic, papillary	1	100.0	0	0.0	1	100.0	
	Total	24	48.0	26	52.0	50	100.0	

In this study, 53.6% of the tumor size less than 10cm expressed positivity, 50% of the tumor size 10-20 cm and 25% of the tumor size more than 20cm was positive for P53.(Table 22)

TABLE 22: CORRELATION OF SIZE WITH P53 POSITIVITY

P53	SIZE			MEAN	STD. DEVIATION	P-VALUE
	<10cm	10-20cm	>20cm			
Positive	15(53.6%)	7(50%)	2(25%)	9.521	4.6097	0.173
Negative	13(46.4%)	7(50%)	6(75%)	12.135	8.3085	

According to FIGO stage, 63.6% of patients with late stage (III & IV) expressed P53 positivity and only 17.6% of patients presented in early stage showed P53 positivity.(Table 23 and Chart 6)

TABLE 23: CORRELATION OF FIGO STAGE WITH P53 POSITIVITY

VARIABLES		P53				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
STAGE	LATE	21	63.6	12	36.4	33	100.0	0.002
	EARLY	3	17.6	14	82.4	17	100.0	
	TOTAL	24	48.0	26	52.0	50	100.0	

Among the histological types, 66.7% of clear cell carcinoma expressed P53 positivity, 55.2% of serous carcinoma, 33.3% of both endometriod and mucinous carcinoma showed P53 positivity. (Table 24)

TABLE-24: CORRELATION OF HISTOLOGICAL TYPES WITH P53 POSITIVITY

VARIABLES		P53				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
HISTOLOGICAL TYPE	Clear Cell	2	66.7	1	33.3	3	100.0	0.512
	Serous	16	55.2	13	44.8	29	100.0	
	Endometrioid	4	33.3	8	66.7	12	100.0	
	Mucinous	2	33.3	4	66.7	6	100.0	

In the present study, P53 positivity was observed in increased frequency of cases with high grade tumors. 23.8% of well differentiated carcinomas(G1), 46.2% of moderately differentiated carcinomas(G2) and 81.3% of poorly differentiated carcinomas(G3) showed positivity for P53. (Table 25 and Chart 7)

TABLE 25: CORRELATION OF GRADE WITH P53 POSITIVITY

VARIABLES		P53				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
GRADE	III	13	81.3	3	18.8	16	100.0	0.002
	II	6	46.2	7	53.8	13	100.0	
	I	5	23.8	16	76.2	21	100.0	
	Total	24	48.0	26	52.0	50	100.0	

22 cases (57.9%) presented with ascites and 2 cases (16.7%) without ascites had showed P53 positivity. (Table 26)

TABLE 26: CORRELATION OF ASCITES WITH P53 POSITIVITY

VARIABLES		P53				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
ASCITIS	Positive	22	57.9	16	42.1	38	100.0	0.013
	Negative	2	16.7	10	83.3	12	100.0	
	Total	24	48.0	26	52.0	50	100.0	

In the present study, expression of P53 positivity is seen in 63.3% of cases with omentum involvement, 25% of patients without omental deposits were observed. (Table 27)

TABLE 27: CORRELATION OF OMENTUM INVOLVEMENT WITH P53 POSITIVITY

VARIABLES		P53				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
OMENTUM	Positive	19	63.3	11	36.7	30	100.0	0.008
	Negative	5	25.0	15	75.0	20	100.0	
	Total	24	48.0	26	52.0	50	100.0	

In this study, the mean CA125 level with P53 positive cases is 371.33 IU and for negative cases mean is 497.221 IU. (Table-28)

TABLE 28: CORRELATION OF CA125 LEVEL WITH P53 POSITIVITY

VARIABLES	P53	N	MEAN	STD. DEVIATION	P-VALUE
CA125	Positive	24	371.33	775.364	0.714
	Negative	26	497.221	1497.65	

CORRELATION OF HER 2 NEU WITH VARIOUS CLINICO PATHOLOGICAL FACTORS

Her2neu positivity is seen in 9% of cases with age less than 40 yrs and 2.6% of cases with age above 40 yrs. The mean age of patient showing Her2neu positivity is 47yrs. (Table 29)

TABLE 29: CORRELATION OF AGE WITH HER2 NEU POSITIVITY

HER 2 NEU	AGE		N	MEAN	STD. DEVIATION	P-VALUE
	<40yrs	>40yrs				
Positive	1(9%)	1(2.6%)	2	47.50	13.435	0.964
Negative	10(91%)	38(97.4%)	48	47.81	9.558	
Total	11	39	50			

In this study, 6.7% of patients with left ovarian mass, 4.3% with right ovarian mass showed Her2neu expression. Bilateral tumors do not show Her2neu positivity. (Table 30)

TABLE 30: CORRELATION OF SITE WITH HER2NEU POSITIVITY

VARIABLES		HER2 NEU				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
SITE	Left	1	6.7	14	93.3	15	100.0	0.675
	Right	1	4.3	22	95.7	23	100.0	
	Bilateral	0	0.0	12	100.0	12	100.0	

Among the gross morphology, Her2neu positivity was observed in 16.7% of cases with purely solid areas, 5.6% of cases with solid and cystic areas.(Table 31)

TABLE 31: CORRELATION OF GROSS WITH HER2NEU POSITIVITY

VARIABLES		HER2 NEU				TOTAL		P-VALUE
		Positive		Negative				
		N	%	N	%	N	%	
GROSS	Solid	1	16.7	5	83.3	6	100.0	0.655
	Solid/ Cystic	1	5.6	17	94.4	18	100.0	
	Cystic, papillary	0	0.0	1	100.0	1	100.0	
	Solid, papillary	0	0.0	15	100.0	15	100.0	
	Solid/Cystic,papillary	0	0.0	6	100.0	6	100.0	
	Multiloculated	0	0.0	4	100.0	4	100.0	

In this study, the average size of the tumor measuring 12.5cm showed positive to Her2neu. (Table 32)

TABLE 32: CORRELATION OF SIZE WITH HER2 NEU POSITIVITY

VARIABLES	HER2 NEU	N	MEAN	STD. DEVIATION	P-VALUE
SIZE	Negative	48	10.813	6.9248	0.737
	Positive	2	12.500	6.3640	

In this study, Her 2 neu positivity was noticed in 6.1% of late stage cases which includes stage III & IV. (Table 33)

TABLE 33: CORRELATION OF STAGE WITH HER2NEU POSITIVITY

VARIABLES		HER2 NEU				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
Stage	Late	2	6.1	31	93.9	33	100.0	0.542
	Early	0	0.0	17	100.0	17	100.0	

Among the histological subtypes, 8.3% of endometrioid type showed positivity and 16.7% of mucinous carcinoma were Her2neu positive.(Table 34)

TABLE 34: CORRELATION OF HISTOLOGICAL TYPE WITH HER2NEU POSITIVITY

VARIABLES		HER2 NEU				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
HISTOLOGICAL TYPE	Mucinous	1	16.7	5	83.3	6	100.0	0.171
	Endometrioid	1	8.3	11	91.7	12	100.0	
	Clear cell	0	0.0	3	100.0	3	100.0	
	Serous papillary	0	0.0	29	100.0	29	100.0	

Her2neu expression is observed in 12.5% of poorly differentiated tumors. Grade I and II tumors does not show Her 2 neu positivity. (Table 35)

TABLE 35: CORRELATION OF GRADE WITH HER2 NEU POSITIVITY

VARIABLES		HER2 NEU				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
GRADE	I	0	0.0	21	100.0	21	100.0	0.162
	II	0	0.0	13	100.0	13	100.0	
	III	2	12.5	14	87.5	16	100.0	

Her 2 neu positivity is observed in 5.3% of cases with ascites. (Table 36)

TABLE-36:CORRELATION OF ASCITES WITH HER2 NEU POSIYIVITY

VARIABLES		HER2 NEU				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
ASCITIS	Positive	2	5.3	36	94.7	38	100.0	0.999
	Negative	0	0.0	12	100.0	12	100.0	
	Total	2	4%	48	96.0	50	100.0	

6.7% of the cases with omentum involvement showed Her2neu positivity.(Table 37)

TABLE 37: CORRELATION OF OMENTUM INVOLVEMENT WITH HER2 NEU POSITIVITY

VARIABLES		HER2 NEU				TOTAL		P-VALUE
		POSITIVE		NEGATIVE				
		N	%	N	%	N	%	
OMENTUM	Positive	2	6.7	28	93.3	30	100.0	0.510
	Negative	0	0.0	20	100.0	20	100.0	
Total		2	4.0	48	96.0	50	100.0	

The mean CA 125 level of 137.63 IU was observed in positive cases. (Table 38)

TABLE 38: CORRELATION OF CA125 WITH HER2 NEU POSITIVITY

VARIABLES	HER2 NEU	N	MEAN	STD. DEVIATION	P-VALUE
CA125	Negative	48	449.26	1219.53	0.722
	Positive	2	137.63	107.15	

CORRELATION OF P53 AND HER2NEU EXPRESSION WITH PROGNOSIS

In this study, prognosis was analyzed for 50 patients for whom IHC was done. Post operatively patients were given 6 courses of cisplatin, cycliphosphamide regimen every 21 days and follow up of the patients were done for the median period of 15 months. 3 patients had pre chemotherapy and continued in postoperative period. Among the 50 patients with epithelial carcinoma, 31 patients (62%) were alive, 16 patients (32%) have died due to recurrence and other general cause and 3 patients (6%) had left the follow up. Among the patients who had survived 3 patients (9.7%) showed recurrence after 12 months. They were given adjuvant chemotherapy .They survived well and further follow up was done. Prognosis of the patients with P53, Her2neu positivity and clinopathological parameters was analyzed with 47 patients. 3 patients who had

lost the follow up were not included to study the odds ratio and relative risk and outcome of the patients.

P53 positivity is observed in 24 cases. Out of this 2 patients had left follow up. 10 patients (45.5%) were alive until the period of study. Those patients with recurrence showed positivity to P53 expression. 12 patients (54.5%) have died. This shows statistically significant association of P53 positivity (p=0.005) with worse survival.

Her 2neu positivity is observed in 2 patients. 1 patient (50%) is alive and 1 patient (50%) died. There is no significant association of Her2neu positivity (p=0.999) with survival of the patients. (Table 39)

Table 39: CORRELATION OF P53 AND HER2NEU EXPRESSION WITH PROGNOSIS

		PROGNOSIS				**TOTAL**		**P-VALUE**
		GOOD		POOR				
		N	%	N	%	N	%	
P53	Positive	10	45.5	12	54.5	22	100.0	0.005
	Negative	21	84.0	4	16.0	25	100.0	
HER2 NEU	Positive	1	50.0	1	50.0	2	100.0	0.999
	Negative	30	66.7	15	33.3	45	100.0	
Total		31	66.0	16	34.0	47	100.0	

STUDY OF PROGNOSTIC IMPACT OF CLINICO-PATHOLOGICAL AND IMMUNOHISTOCHEMICAL PARAMATERS.

In the present study, influence of these variables with outcome of the patients was evaluated. Results were reported as relative risk and 95% confidence interval. P value <0.005 is considered significant.

In this study, 42.1% of the patients of age above 40 had decreased survival whereas all patients less than 40yrs had survived well. (Table 40 and Chart 8)

Table 40: ASSOCIATION OF AGE GROUP WITH SURVIVAL

		SURVIVAL STATUS				**TOTAL**		**P-VALUE**
		NON SURVIVAL		SURVIVAL				
		N	%	N	%	N	%	
Age group (yrs)	> 40	16	42.1	22	57.9	38	100.0	
	≤40	0	0.0	9	100.0	9	100.0	0.017
Total		16	34.0	31	66.0	47	100.0	

48.4% of the patients with late stage disease had died whereas 6.3% of the patients with early stage had decreased survival. (Table 41 and Chart 9)

Table 41: ASSOCIATION OF STAGE OF DISEASE WITH SURVIVAL

		SURVIVAL STATUS				TOTAL	
		NON SURVIVAL		SURVIVAL			
		N	%	N	%	N	%
Stage	Late	15	48.4	16	51.6	31	100.0
	Early	1	6.3	15	93.8	16	100.0
Total		16	34.0	31	66.0	47	100.0

Serous carcinoma has worst survival than other histological types. 42.9% of serous carcinoma patients have not survived whereas only 21.1% of the patients had poor survival in other types. (Table 42)

TABLE 42:ASSOCIATION OF HISTOLOGICAL TYPE WITH SURVIVAL

		SURVIVAL STATUS				TOTAL	
		NON SURVIVAL		SURVIVAL			
		N	%	N	%	N	%
Histological type	Serous	12	42.9	16	57.1	28	100.0
	Others	4	21.1	15	78.9	19	100.0
Total		16	34.0	31	66.0	47	100.0

Clear cell carcinoma has worst survival than the other histological type (66.7%). (Table 43)

TABLE 43:ASSOCIATION OF HISTOLOGICAL TYPE WITH SURVIVAL

		SURVIVAL STATUS				TOTAL	
		NON SURVIVAL		SURVIVAL			
		N	%	N	%	N	%
Histological type	Clear cell	2	66.7	1	33.3	3	100.0
	Others	14	31.8	30	68.2	44	100.0
Total		16	34.0	31	66.0	47	100.0

In this study, 60% of the patients with high grade carcinoma and only 21.9% of the cases with low grade tumor had poor survival. (Table 44 and Chart 10)

TABLE 44: ASSOCIATION OF GRADE WITH SURVIVAL

		SURVIVAL STATUS				TOTAL	
		NON SURVIVAL		SURVIVAL			
		N	%	N	%	N	%
Grade	High	9	60.0	6	40.0	15	100.0
	Low	7	21.9	25	78.1	32	100.0
Total		16	34.0	31	66.0	47	100.0

44.4% of the patients presented with ascites had died. All the patients (100%) without ascites were alive. (Table 45 and Chart 11)

TABLE 45: ASSOCIATION OF ASCITES WITH SURVIVAL

		SURVIVAL STATUS				TOTAL		P-VALUE
		NON SURVIVAL		SURVIVAL				
		N	%	N	%	N	%	
ASCITIS	Positive	16	44.4	20	55.6	36	100.0	0.009
	Negative	0	0.0	11	100.0	11	100.0	
Total		16	34.0	31	66.0	47	100.0	

54.5% of the P53 positive patients had worse survival, whereas only 16% of the patients with P53 negative had worse survival. (Table 46 and Chart 12)

TABLE 46: ASSOCIATION OF P53 POSITIVITY WITH SURVIVAL

		SURVIVAL STATUS				TOTAL	
		NON SURVIVAL		SURVIVAL			
		N	%	N	%	N	%
P 53	Positive	12	54.5	10	45.5	22	100.0
	Negative	4	16.0	21	84.0	25	100.0
Total		16	34.0	31	66.0	47	100.0

50% of the Her2neu positive patient had decreased survival, only 33.3% of the negative patients had decreased survival. (Table 47)

TABLE 47: ASSOCIATION OF HER2NEU POSITIVITY WITH SURVIVAL

		SURVIVAL STATUS				TOTAL	
		NON SURVIVAL		SURVIVAL			
		N	%	N	%	N	%
HER 2 NEU	Positive	1	50.0	1	50.0	2	100.0
	Negative	15	33.3	30	66.7	45	100.0
Total		16	34.0	31	66.0	47	100.0

In this study correlation of the survival of the patients with clinicopathological and immunohistochemical parameters were analysed by calculating RR, CI and P-value. (Table 48)

TABLE 48: RELATIVE RISK AND P-VALUE FOR SURVIVAL ANALYSIS OF CLINICOPATHOLOGICAL AND IHC PARAMETERS

FACTORS	**RR**	**95%CI**	**P- VALUE**
Age >40 vs<40	-	-	0.017
Stage Late vs early	7.742	1.1-53.5	0.004
Grade High vs low	2.743	1.3-5.9	0.010
Type Serous vs others Clearcell vs others	 2.036 2.095	 0.8-5.4 0.8-5.2	 0.122 0.216
Ascites Presence vs absence	-	-	0.009
P53 Positive vs negative	3.409	1.2-9	0.005
Her 2 neu Positive vs negative	1.500	0.3-6.3	0.995

SEROUS CYSTADENOCARCINOMA

Fig -1.GROSS - Solid and cystic areas

Fig-2 solid, cystic with papillary areas

MUCINOUS CARCINOMA

FIG-3. fleshy white solid and cystic mucinous nodules

ENDOMETRIOID CARCINOMA

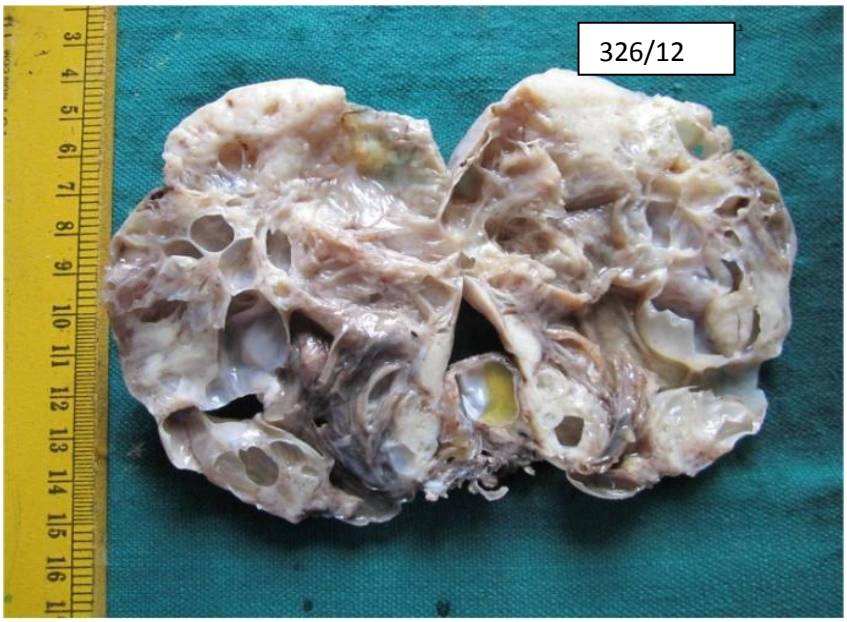


FIG-4. Solid and small cystic areas honeycomb appearance

ENDOMETRIOID CARCINOMA

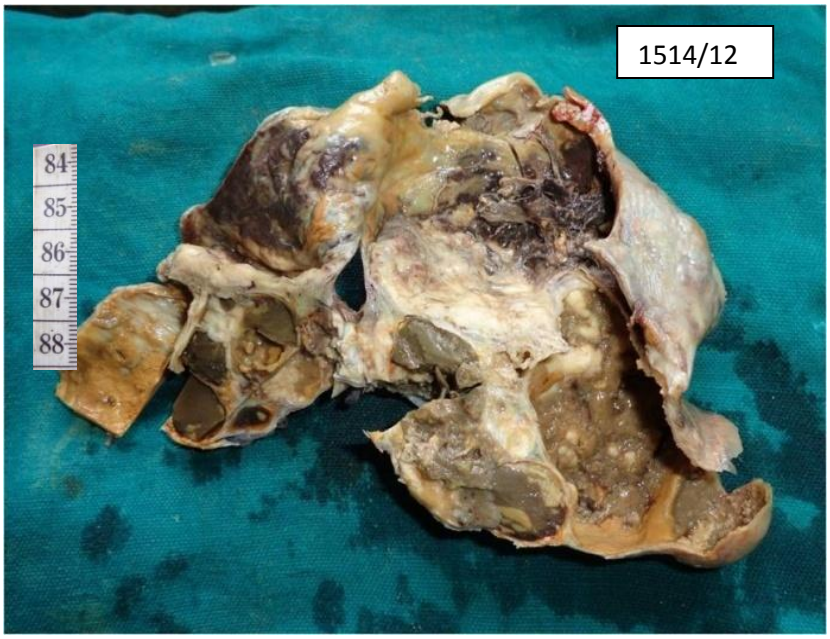


FIG-5. Solid and cystic areas with hemorrhage and necrosis

CLEAR CELL CARCINOMA

Fig-6.Grey white solid

SEROUS CARCINOMA GRADE -I

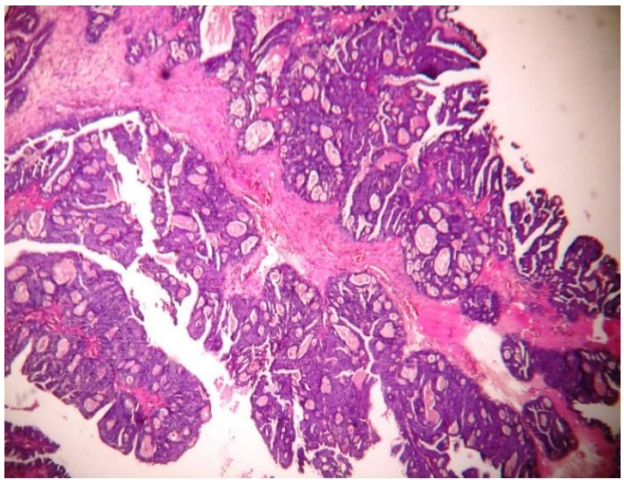


FIG-7.H&E.Well differentiated papillae (10X)

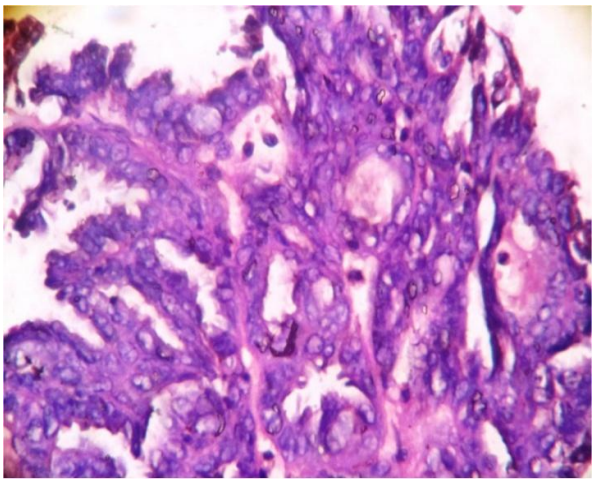


FIG-8.H&E.Papillae showing tumor cells with nuclear pleomorphism (40X)

SEROUS CARCINOMA-GRADE II

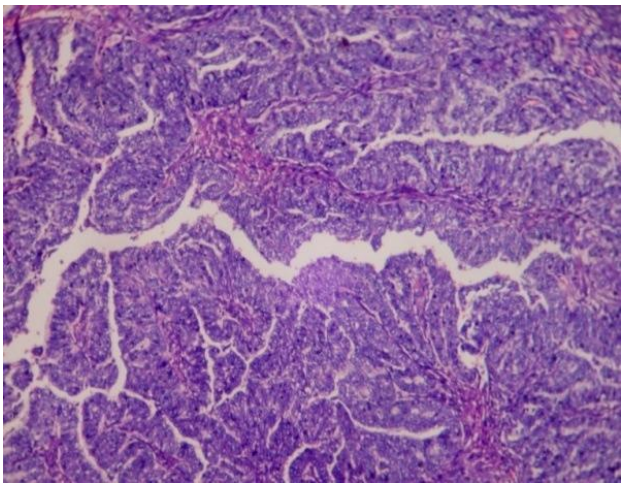


FIG-9.H&E.Moderately differentiated papillae and solid sheets. (10X)

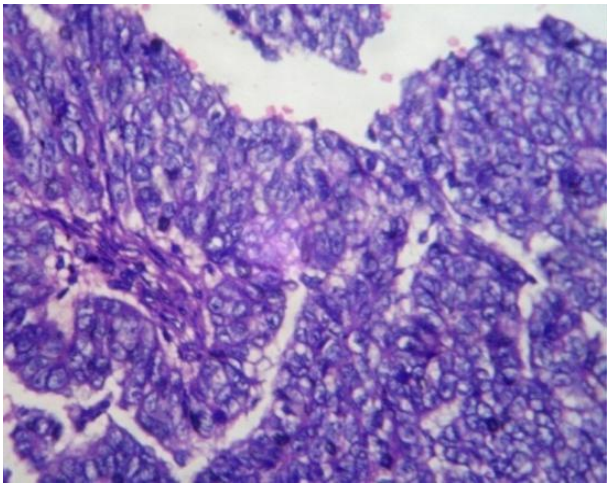


FIG-10.H&E.Malignant epithelial cells with Nuclear pleomorphism (40X)

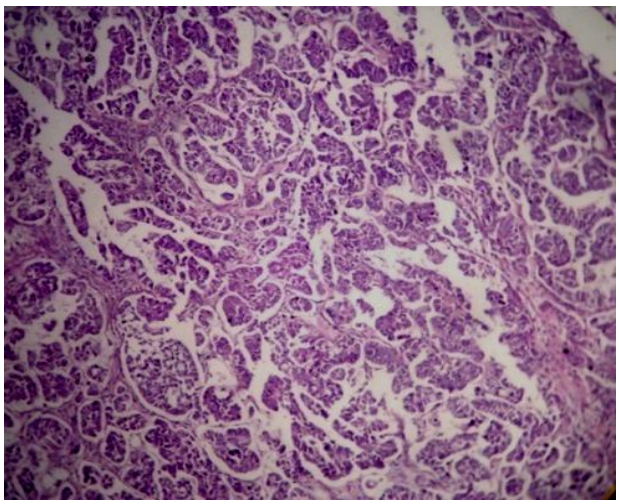


FIG-11.H&E.Serous carcinoma complex papillae (10X)

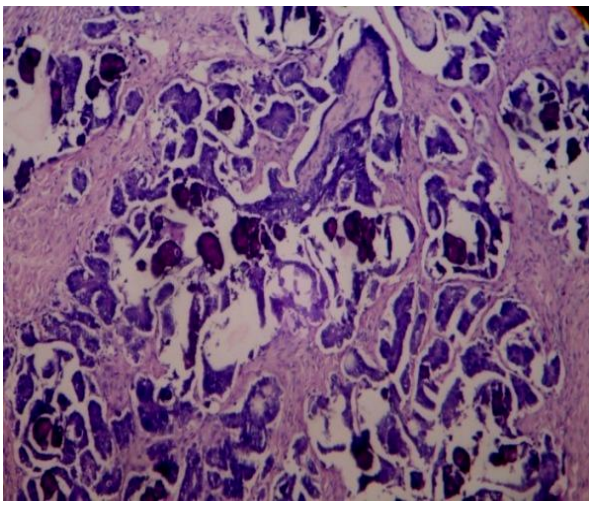


FIG-12. H&E.Serous carcinoma papillae with psommoma bodies. (40X)

SEROUS CARCINOMA- GRADE III

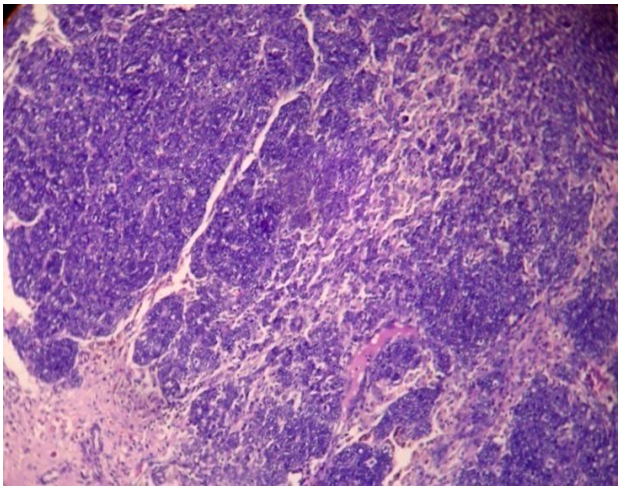


FIG-13. H&E. Poorly differentiated cells in solid sheets. (10X)

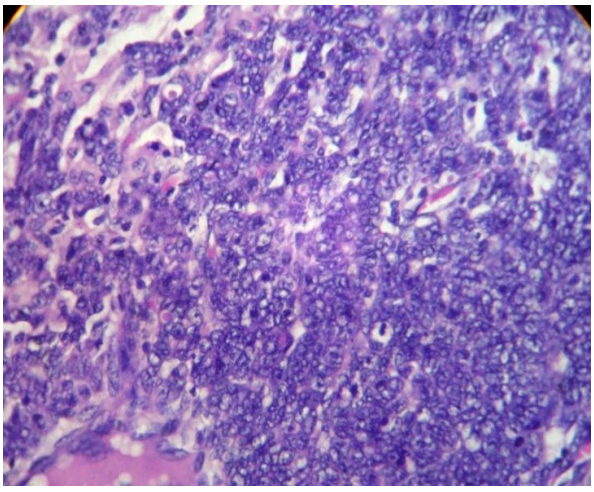


FIG-14. H&E. Solid growth, marked nuclear atypia and high mitotic activity.(40X)

MUCINOUS CARCINOMA

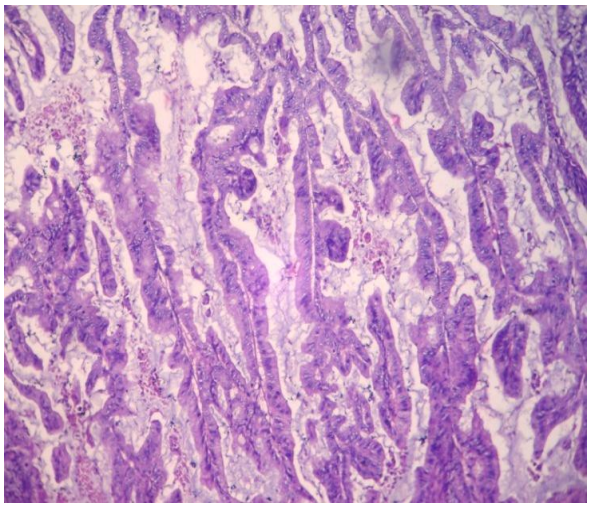


FIG-15. H&E.Confluent growth of complex interconnecting papillae. (10X)

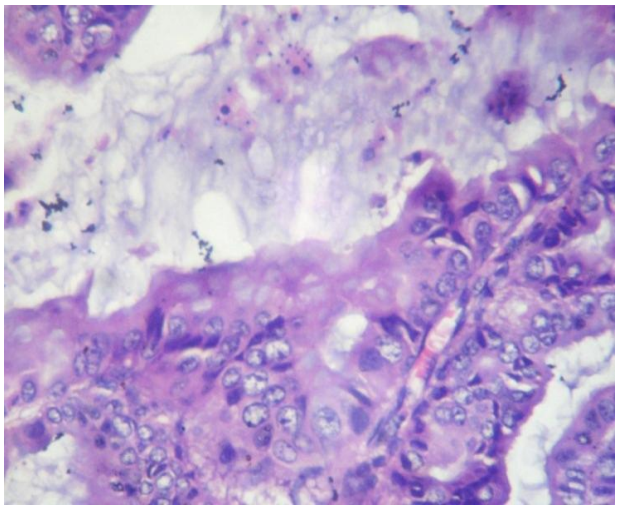


FIG-16. H&E. Epithelial cells showing nuclear atypia with mucinous background.(40X)

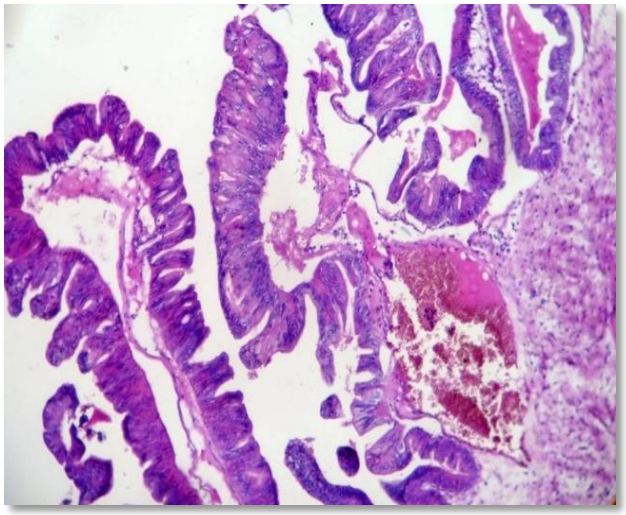


FIG-17. H&E.Glands lined by epithelium with tallcolumnar cells.(10X)

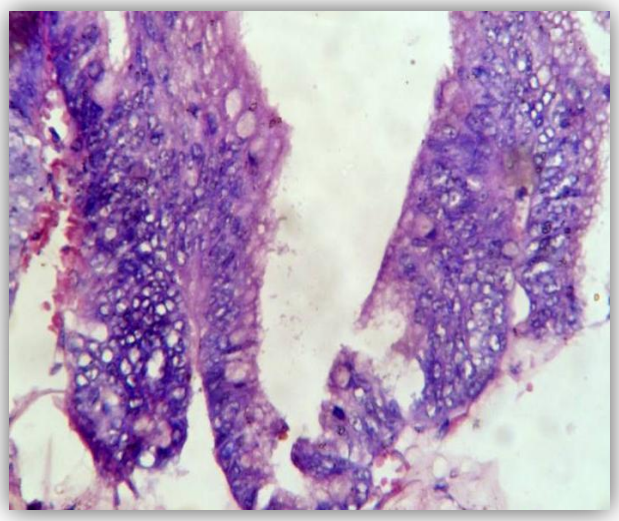


FIG-18. H&E.Increased layering of cells with stratification and nuclear atypia.(40X)

ENDOMETRIOID CARCINOMA

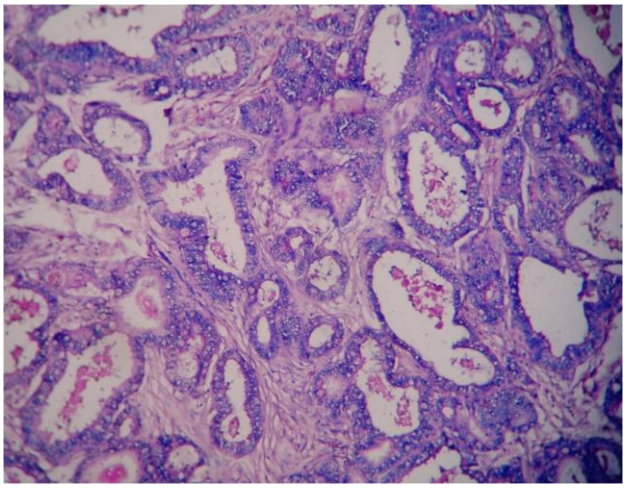


FIG-19. H&E. Tumor with well differentiated endometrial type glands. (10X)

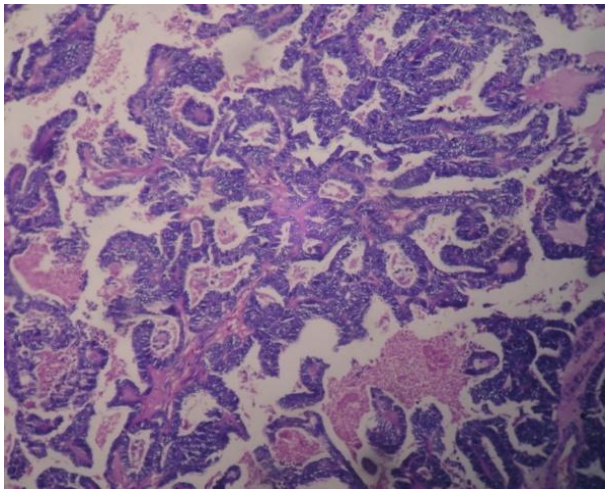


FIG-20. H&E. Glands with back to back arrangement. (10X)

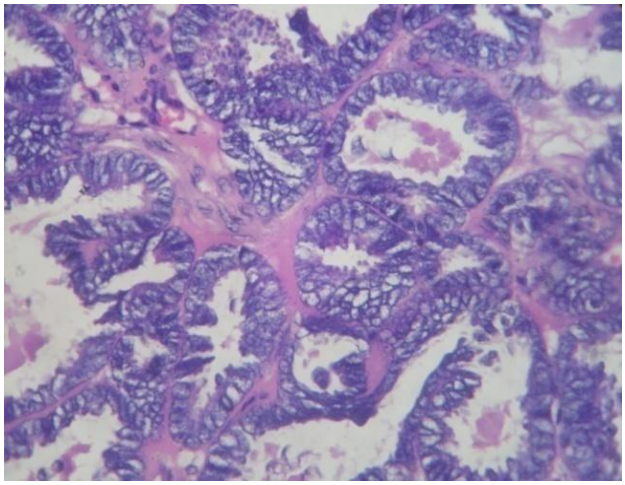


FIG-21.H&E.Glandular epithelial cells with nuclear atypia. (40X)

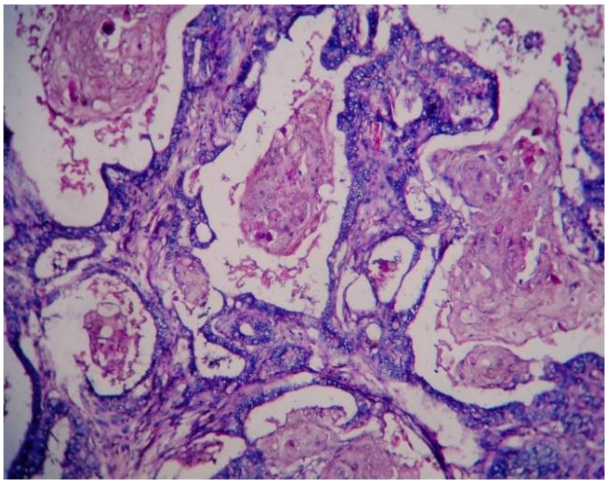


FIG-22.H&E.Well differentiated endometrioid carcinoma with squamous metaplasia.(10X)

CLEAR CELL CARCINOMA

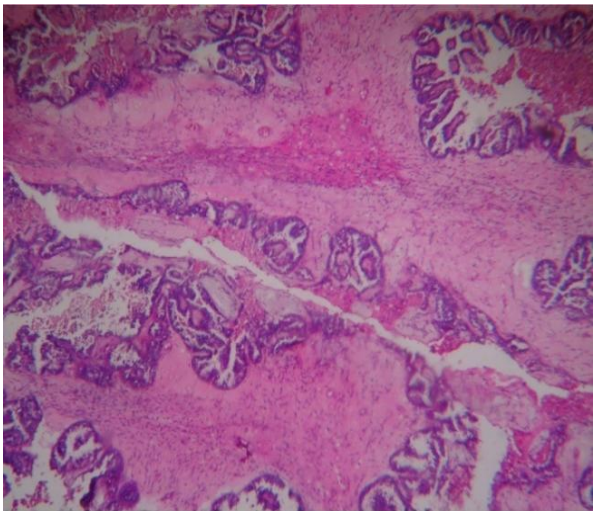


FIG-23.H&E.Malignat epithelial cells arranged in papillary pattern. (10X)

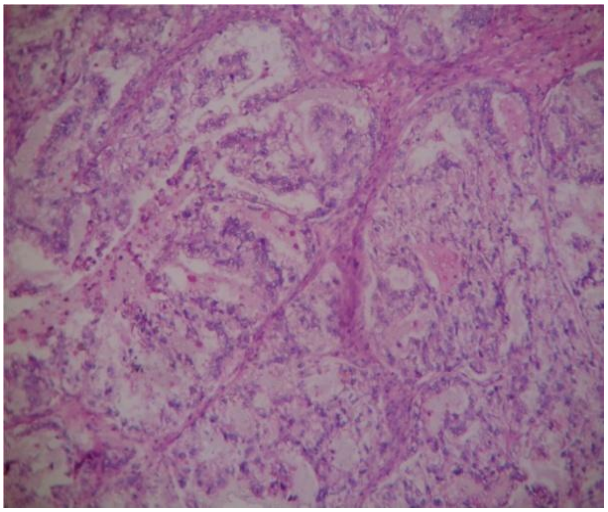


FIG-24.H&E.Malignat epithelial cells arranged in sheets pattern. (10X)

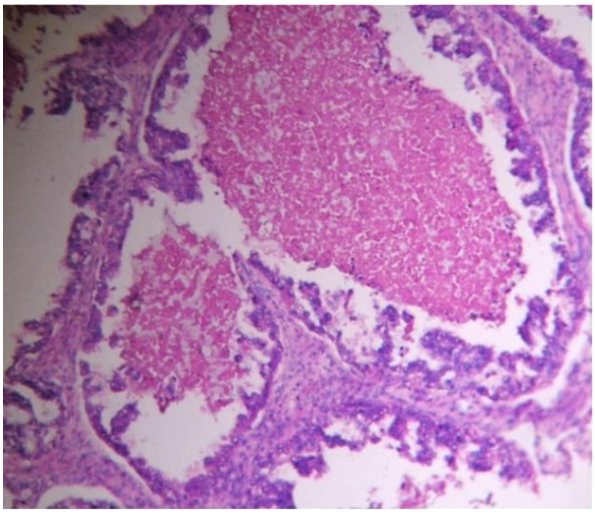


FIG-25.H&E.Tubulocystic pattern lined by hobnail cells. (10X)

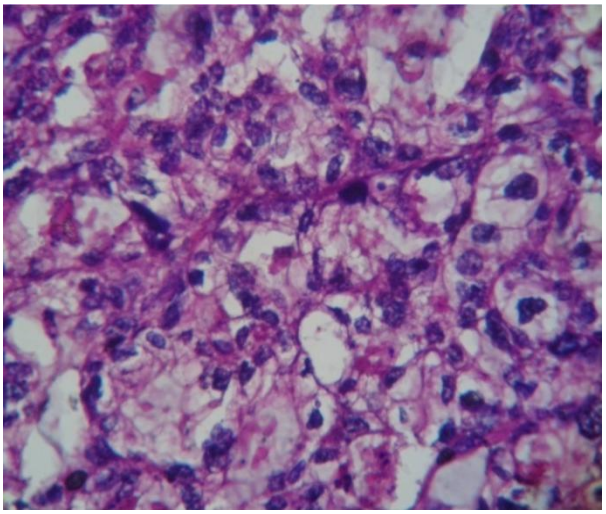


FIG-26. H&E. Polyhedral cells with clear cytoplasm and pleomorphic nuclei. (40X).

HER 2NEU POSITIVITY

ENDOMETRIOID CARCINOMA GRADE-III

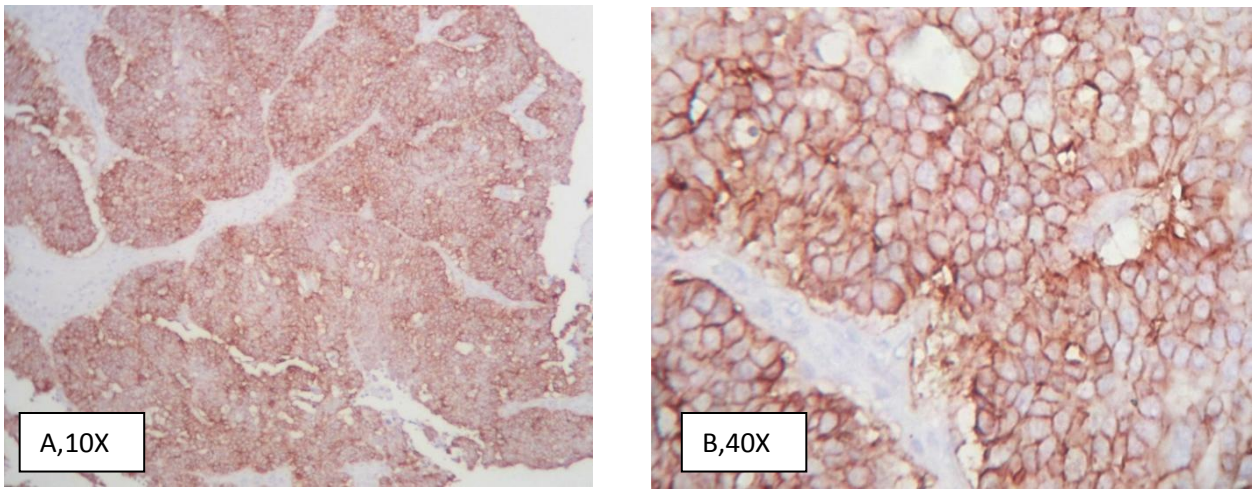


FIG-27. A,B. IHC. Strong cytoplasmic membrane staining for Her 2 neu.

MUCINOUS CARCINOMA

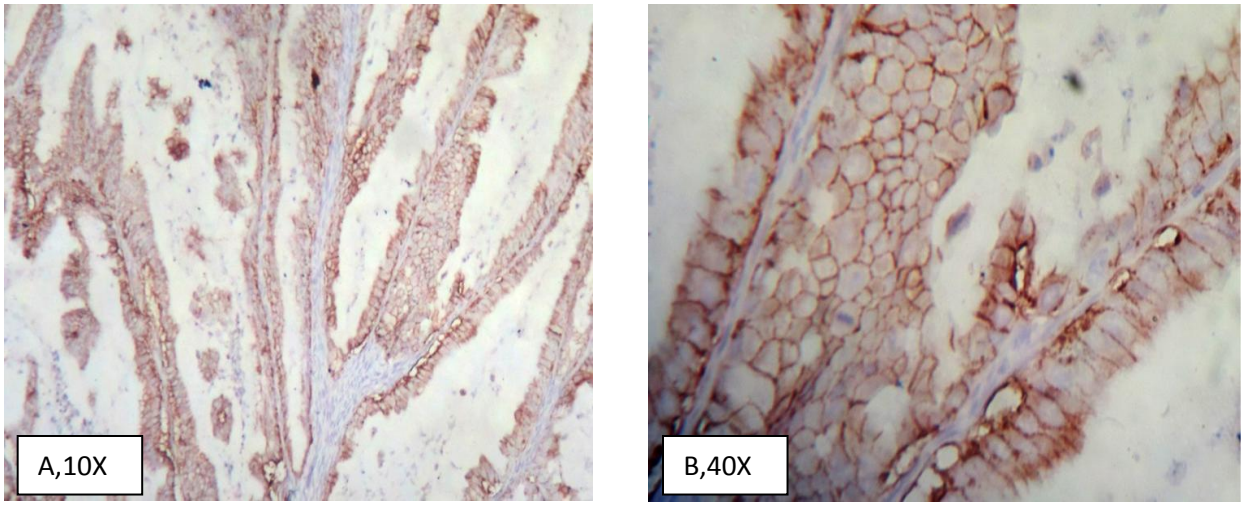


FIG-28. A,B.IHC. Strong cytoplasmic membrane staining for Her 2 neu.

P53 POSITIVE

SEROUS CARCINOMA

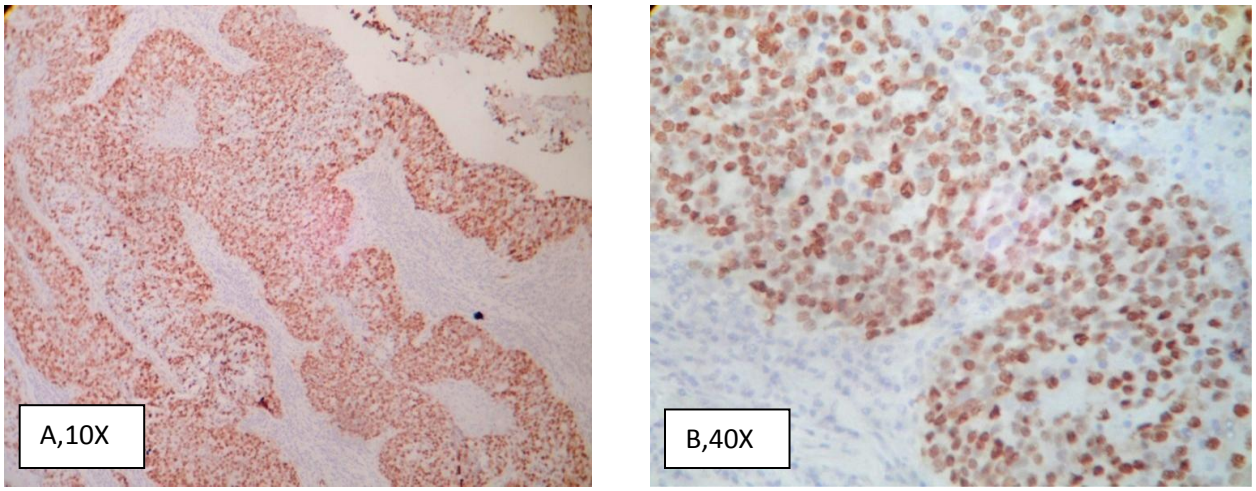


FIG-29. A,B.IHC. Papillae with strong nuclear staining for P 53

CLEARCELLCARCINOMA

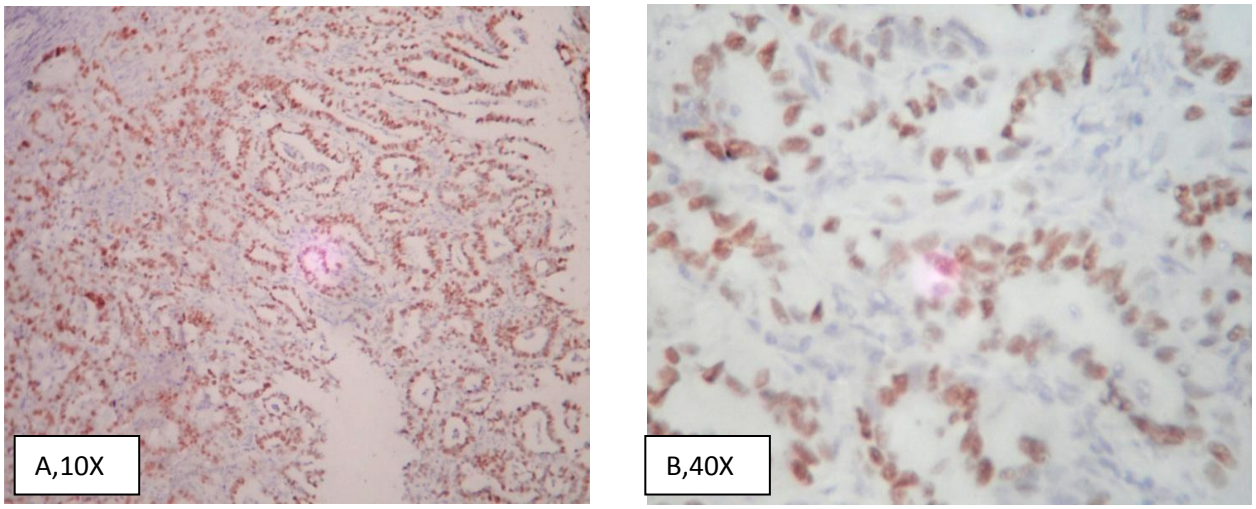


FIG-30. A,B.IHC . Tubular glands with strong nuclear staining for P53

P53 POSITIVE

MUCINOUS CARCINOMA

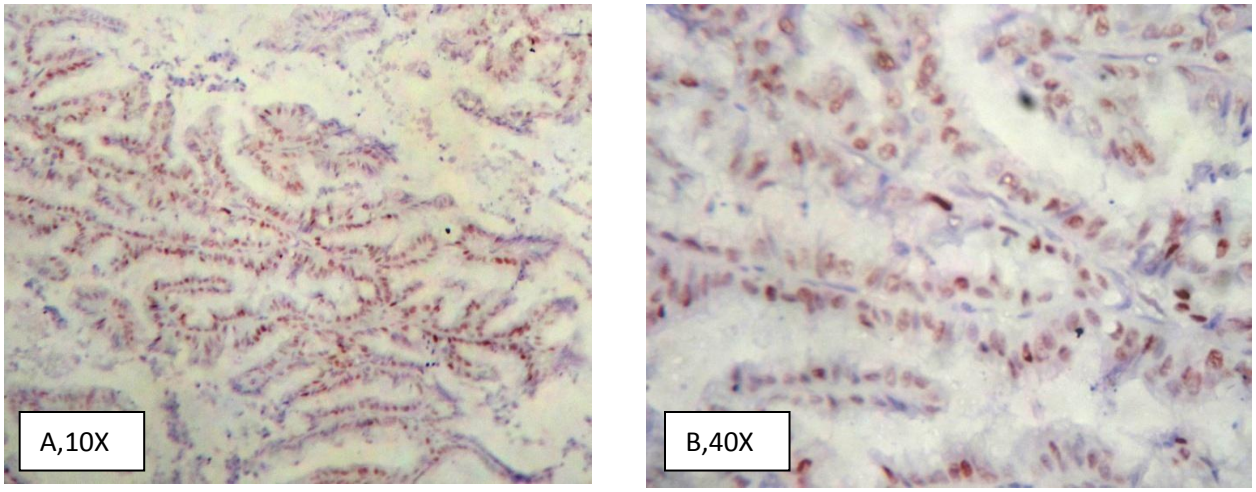


FIG-31. A,B. IHC. Tall columnar cells with strong nuclear staining for P

ENDOMETRIOID CARCINOMA

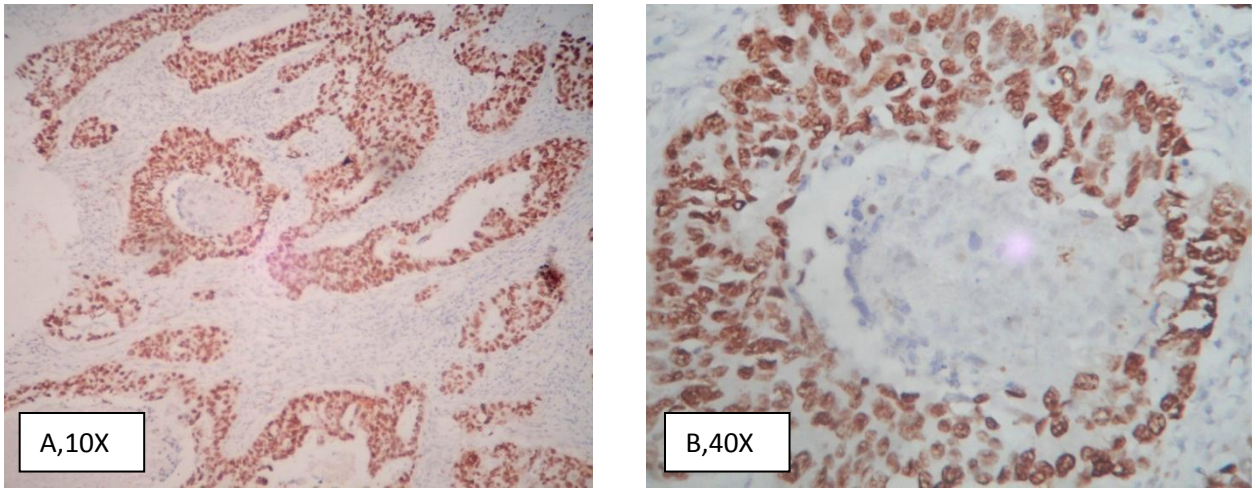


FIG-32. A,B. IHC . Glands with strong nuclear staining for P 53

CHART-1 DISTRIBUTION OF OVARIAN CARCINOMA WITH SITE

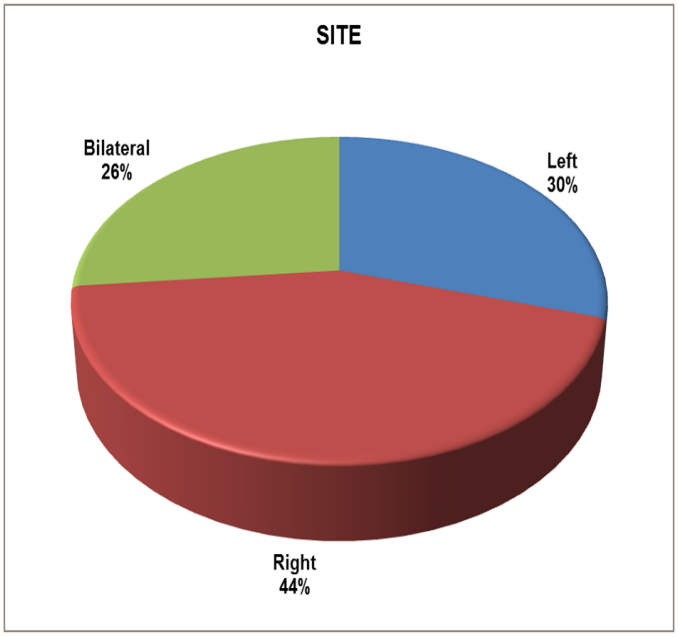


CHART-2 DISTRIBUTION OF OVARIAN CARCINOMA WITH GROSS MORPHOLOGY

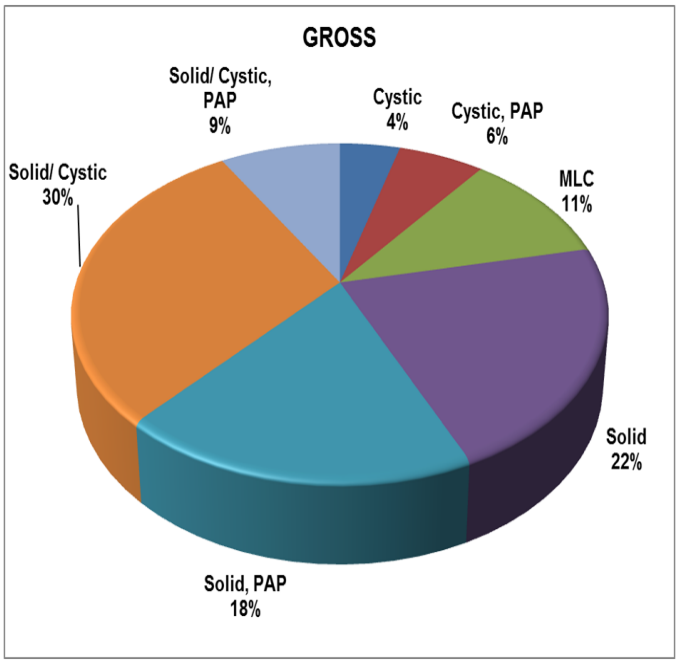


CHART-3 DISTRIBUTION OF OVARIAN CARCINOMA WITH HISTOLOGICAL TYPE

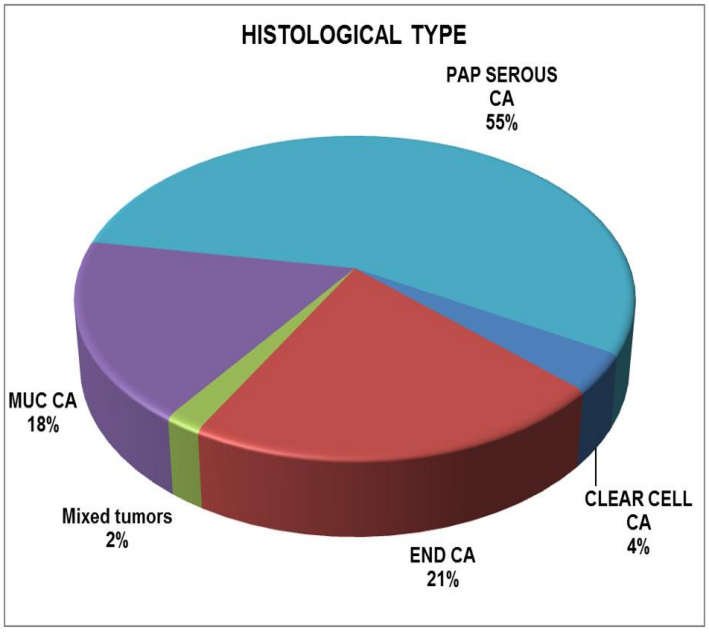


CHART-4 DISTRIBUTION OF OVARIAN CARCINOMA WITH GRADE

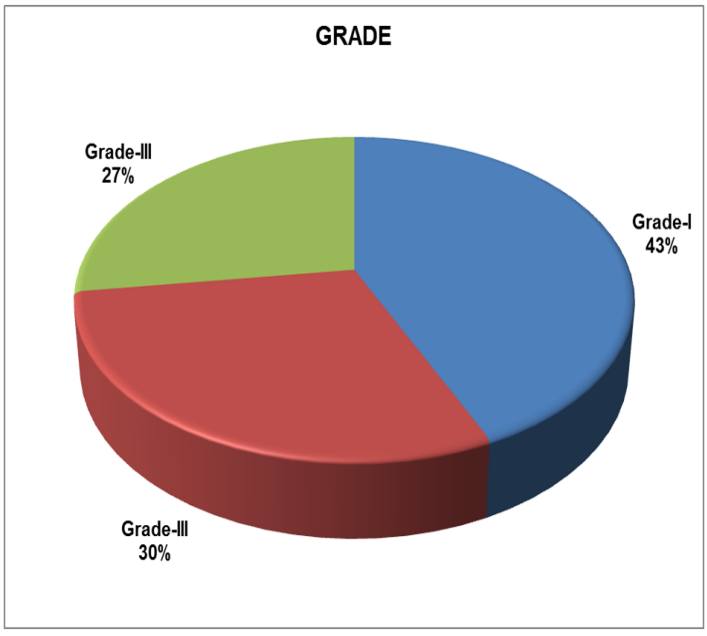


CHART-5 DISTRIBUTION OF OVARIAN CARCINOMA WITH STAGE

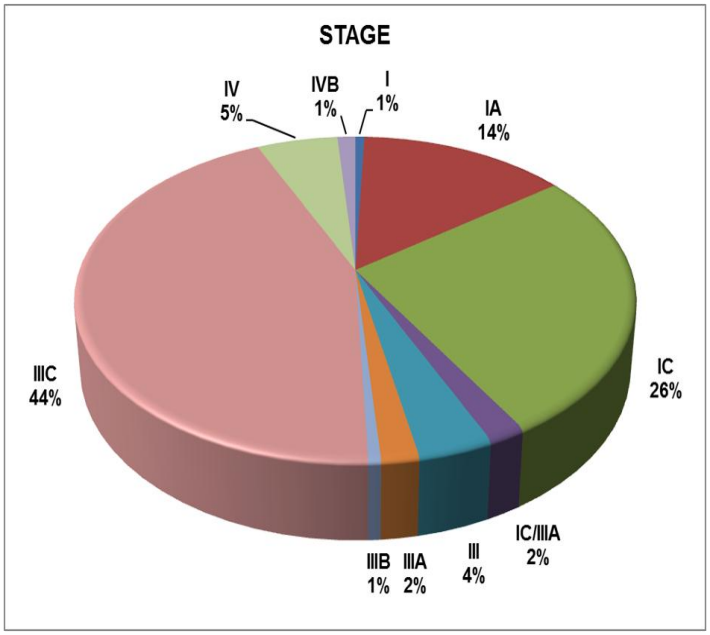


CHART-6 DISTRIBUTION OF P53 POSITIVITY WITH STAGE

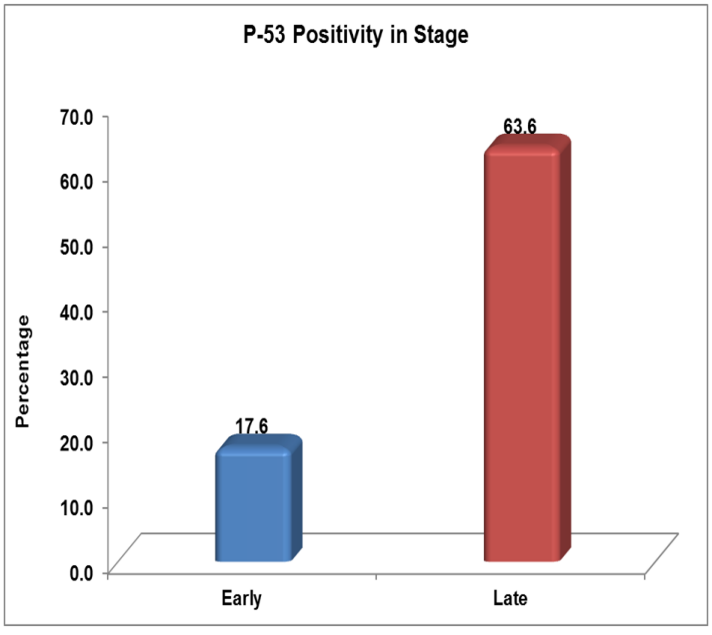


CHART-7 DISTRIBUTION OF P53 POSITIVITY WITH GRADE

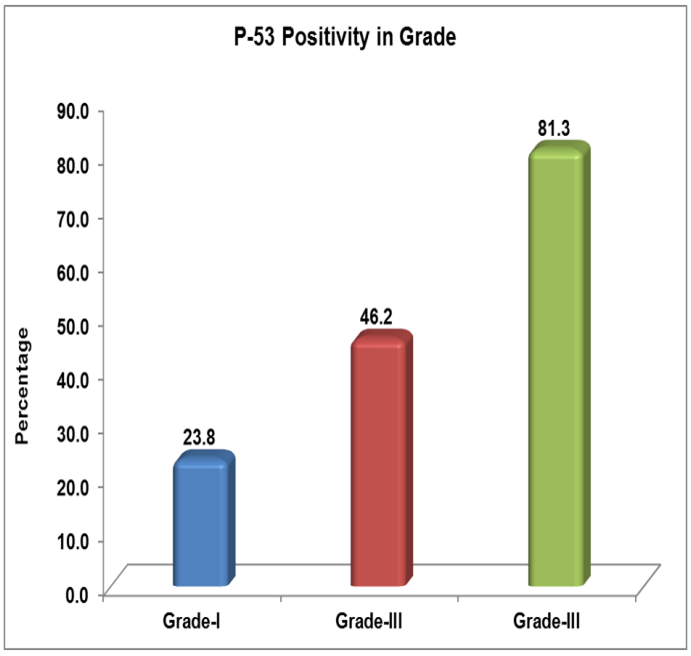


CHART-8 ASSOCIATION OF AGE GROUP WITH POOR SURVIVAL

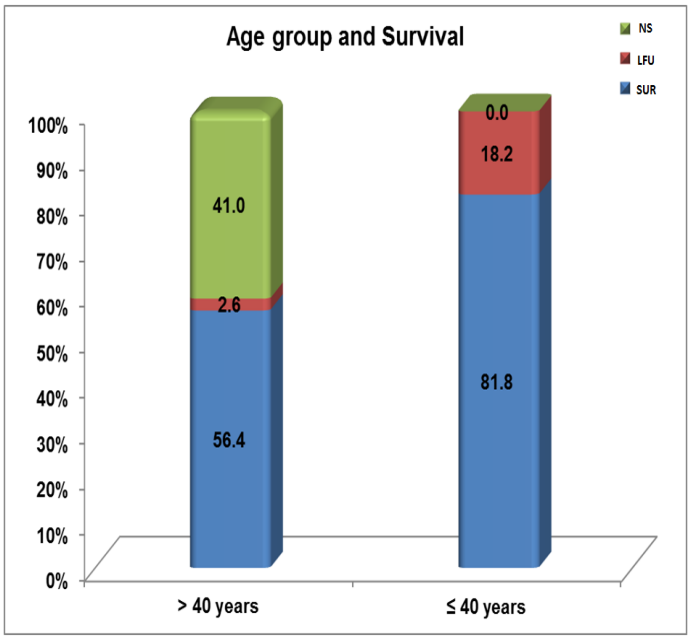


CHART-9 ASSOCIATION OF STAGE WITH POOR SURVIVAL

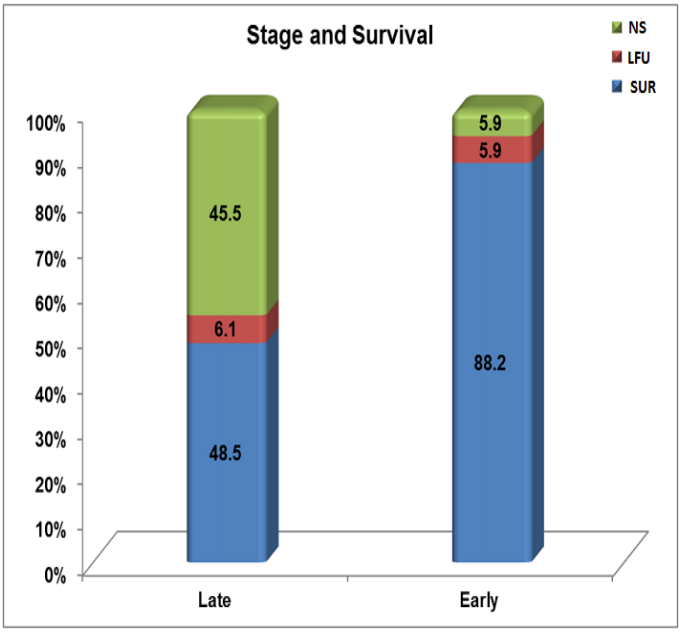


CHART-10 ASSOCIATION OF GRADE WITH POOR SURVIVAL

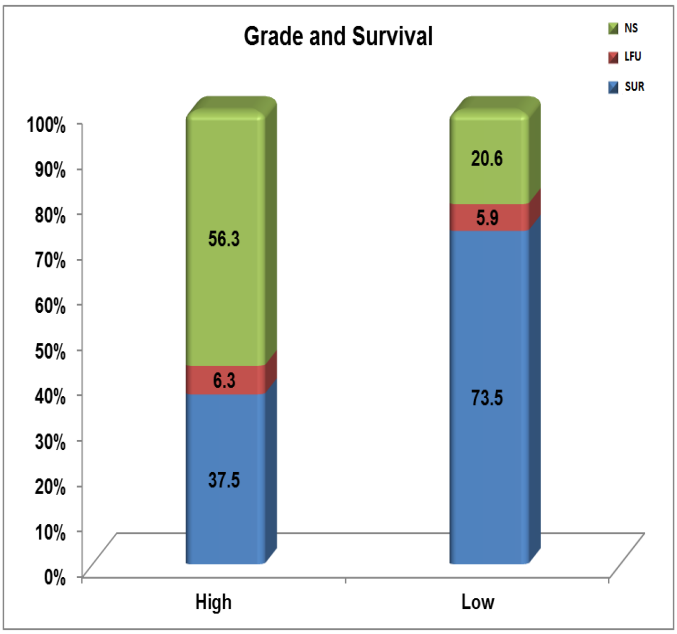


CHART-11 ASSOCIATION OF ASCITES WITH POOR SURVIVAL

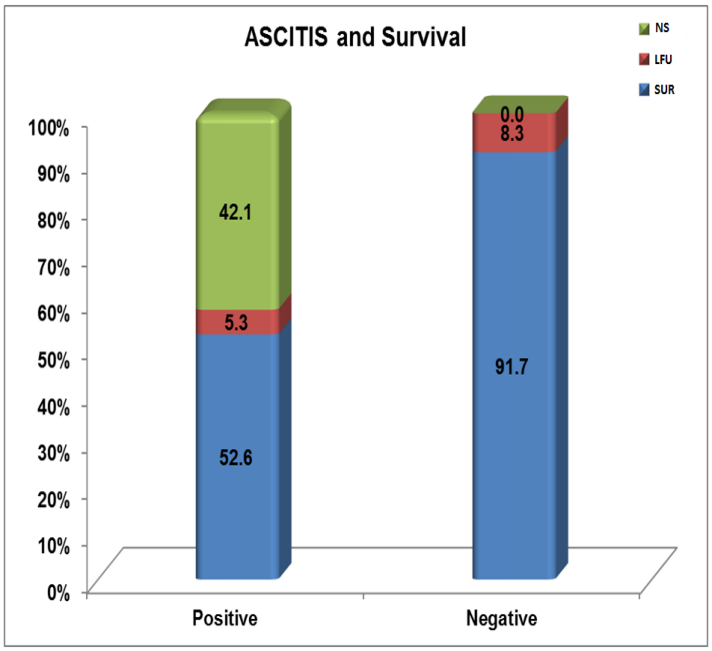
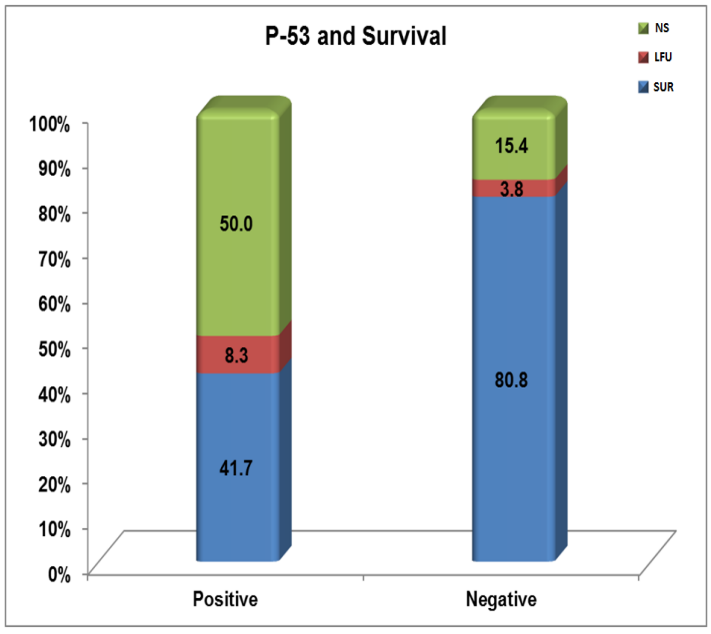


CHART-12 ASSOCIATION OF P53 WITH POOR SURVIVAL



DISCUSSION

DISCUSSION

Ovarian cancer is one of the leading causes of death among all gynaecological malignancies. In India, Ovarian cancer is the most lethal gynecologic malignancy which ranks 2nd after cervical cancer. In Chennai, ovarian cancer stands in the third position[3].

Due to lack of effective screening methods, 70% of the epithelial carcinomas are diagnosed only at an advanced stage[74]. Various new biological markers have been studied as prognostic and predictive factors for the evaluation of the biological behavior of ovarian cancer and to improve treatment planning. Among these, immunohistochemical staining of P53 and Her2neu have been proposed to be of prognostic value. In the present study potential impact of the expression of P53 and Her2neu protein on the outcome of patients with malignant epithelial ovarian tumors and for their targeted therapy was analysed.

Immunohistochemical evaluation was done in 50 cases of epithelial ovarian carcinomas and attempted to correlate the P53 and Her2neu expression with the known prognostic factors like age, presence of ascites, stage, grade and histological type of ovarian cancers. Follow up of the patients was done to assess the survival of the patients.

Madras Medical College- Institute of Obstetrics & Gynaecology, Egmore & Institute of Social Obstetrics and Kasthurbai Gandhi Hospital, Triplicane being a tertiary referral centre, total number of 850 cases with ovarian cancers was reported in the year 2008-2012. Among the entire ovarian specimens received for histopathological examination, 638 cases (75.1%) of the cases were reported to be surface epithelial ovarian tumors and 162(25.4%) of the cases were malignant.

In 2008, WHO had reported 224,747 new cases of epithelial ovarian carcinomas in the world population. Among them, approximately 43% was diagnosed in women above 60 years[75]. Epithelial ovarian carcinoma was diagnosed after menopause in North America. In USA approximately 50% of epithelial ovarian carcinoma cases were diagnosed at the age of 60 years.[76]

In this study, the age of epithelial ovarian cancer patients ranged from 22 to 70 years with the mean age of 47 years. The highest incidence of epithelial ovarian carcinoma (42%) occurred in 4th to 5 th decade and it constitutes only 6% in 6 th decade. This is in contrast with the study done by Murthy NS et al[14] who observed incidence in the peak age of 55-64yrs and another study done by J K Chan, et al[15] who reported it as a disease of post menopausal age. 5.6% of serous carcinomas occurred in 2nd to 3rd decades of life which is in contrast to the study done by Nandakudi SM[14] who observed serous tumors are rare in 2nd to 3 rd decade.

COMPARISION OF DISTRIBUTION OF TUMORS WITH SITE

In the present study, 26.5% of the epithelial tumors showed bilateral involvement which is similar to the study done by Marcela F Paes, et al [54] who observed 29% of bilaterality.

Also 31% of serous carcinomas are bilateral and 86.2% of mucinous carcinomas are unilateral which is in accordance to literature[22]. High frequencies of cases with endometrioid and clearcell carcinoma were unilateral.

COMPARISION OF DISTRIBUTION OF TUMORS WITH SUBTYPES

According to literature,[64] Serous carcinomas constitutes 30%, mucinous 15%,endometriod 20% and clear cell 2-5% of all ovarian tumors . It showed concordance to study done by Marcela F Paes, et al [54] who showed 30% of serous carcinomas, 13% of mucinous and endometriod carcinoma, 2% of clear cell carcinoma.

In this study serous carcinomas constitutes highest percentage of 55.6% when compared to other types of epithelial tumors followed by endometriod carcinoma (21%) which is similar to the finding observed by Ioka A et al[77] and Rangel et al[78]. Ioka A et al, reported that serous carcinoma is the most common histological type. Rangel et al, reported endometriod as second most common tumor among the epithelial ovarian carcinoma.

COMPARISION OF DISTRIBUTION WITH GROSS MORPHOLOGY

In general, ovarian tumors grossly show various morphology. Serous carcinomas show predominant areas of solid with few cystic areas, papillary excrescences are more common in serous carcinomas, mucinous carcinomas show multiloculated cysts.

In this study, among the serous carcinomas 28% showed solid areas with papillary excrescences, 26% presented as a solid and cystic pattern, 22% cases are purely solid. Only 2 % cases presented as purely cystic. 48.3% of mucinous carcinoma presented as a multiloculated cysts compared to other types. 44 % of endometrioid type showed solid with cystic areas predominantly, 35.3% of cases were purely solid. Clear cell carcinoma showed varying morphology like solid, solid cystic, solid with papillary excrescences. This is in accordance to the findings observed by Kurman et al. [22]

COMPARISION OF DISTRIBUTION WITH OVARIAN CANCER SIZE

Among the various histological types, serous carcinomas originate from serous or cortical inclusion cyst. They are usually small and asymptomatic, because of this they present only at the advanced stage. Mucinous carcinomas are large multiloculated cyst, due to this they are presented with abdominal distension and diagnosed earlier.

Robert J. Kurman, M.D.et al [27], in their study on origin and pathogenesis of ovarian carcinoma showed that mucinous carcinomas are large with median size of 9cm, ranges from 5-30cm. Present study is in accordance to above finding with mean size of 10cm and range from 7 cm to 30 cm. Similarly, increased frequency of serous carcinomas presented as a smaller mass and range from 5cm to 15 cm which is similar to finding observed by Kurman et al.

Due to lack of effective screening programme and since patients are asymptomatic, ovarian carcinomas are diagnosed at the advanced stage. In this study, 43.2% of patients presented at stage I , 50% of patients diagnosed at stage III and 6.8% at stage IV. Values of stage I & III were similar to the finding observed by Kim et al[79], Ali-Fehmi R et al[80], Badiglian Filho L et al[81], Derchain S et al[82], Marcela F Paes et al[54].(Table 49)

TABLE 49: COMPARISION OF OVARIAN CANCER STAGE DISTRIBUTION

	STAGE 1	**STAGE III**
Kim et al[79]	39%	42.7%
Ali-Fehmi et al[80]	37%	43%
Badiglial Filho et al[81]	26.3%	42%
Derchain et al[82]	34%	51%
Marcela F Paes et Al[54]	29%	56.2%
Current Study	43.2%	50%

COMPARISION OF OVARIAN CANCER GRADE DISTRIBUTION

In this study, grade 1 carcinomas were more common than the other grades of distribution. 43.2% of the tumors showed well differentiation. This is in contrast to the study conducted by Marcela F Paes et al[54] who noticed the prevalence of grade II differentiation. Present study also showed increased number of serous carcinoma with grade II differentiation, mucinous carcinomas with grade I, all cases of clear cell carcinomas were poorly differentiated.

COMPARISION OF DISTRIBUTION OF OVARIAN CANCER WITH ASCITES

In this study, presence of ascites is seen in all cases of clear cell carcinoma and 85.5% of serous carcinoma and 61% of endometrioid carcinoma than the other types. Also 95.5% of high grade tumors presented with ascites than the low grade. This is in accordance to study done by Yoshimura S, et al[56] who observed presence of ascites in serous carcinoma and in high grade carcinomas.

COMPARISION OF DISTRIBUTION OVARIAN CANCER WITH CA125 LEVEL.

Mary T Sylvia et al [83], had observed that 27.56% of carcinomas showed normal CA125 level. Increased level is noted in advanced stage cases with the median of 275 IU. In this study, 10% of cases have normal CA125 level. It shows

exponential increase in advanced stage carcinomas ranging from 13.9 IU to 7600 IU with median level of 129 IU which is similar to the finding observed by Zorn et al[84] who reported 7.6% of malignant cases with normal CA125 level. This is in contrast to finding observed by Mary T Sylvia et al[83].

COMPARISON OF P53 AND HER2NEU EXPRESSION IN WORLD STATISTICS

In this study the expression of P53 and Her 2 neu was observed in 48% and 4% cases respectively. The proportion of P53 expresssion is similar to the studies conducted by Felip et al[60], J C Mark et al[85], Mary T Sylvia et al[83], Wood-Yee Chan[6] et al. This is in contrast to several studies conducted by S.Camilleri-Broet et al[23], Vassiliki et[86] al, showing 70% of P53 expression .

In the present study, Her 2neu expression is noted in 4% of cases. Other cases did not show Her2neu expression. These cases were counter checked by standard laboratory to rule out technical error since there is wide variation in the positivity. Observed results were in accordance to the study conducted by Marianne Tuefferd et al[87].

In contrast, several studies on Her2neu expression show positivity ranges from 6% to 38%. This fluctuation may be due to different techniques used, small study group and varying characteristics of the studied cases. (Table 50)

TABLE 50: COMPARISON OF P53 AND HER2NEU EXPRESSION IN WORLD STATISTICS

	P53 POSITIVE	P53 NEGATIVE	HER2NEU POSITIVE	HER2 NEU NEGATIVE
Camilleri-Broet et al[23]	71%	29%	16%	84%
Mary T Sylvia et al[83]	57%	43%	21%	79%
Vassiliki et al[86]	70.5%	29.5%	18%	82%
Neilsen J S et al[88]	53%	47%	35%	65%
J.R.Marks[85]	50%	50%	NA	NA
Wood-Yee Chan et al[6]	54%	46%	NA	NA
Berchuk et al[89]	NA	NA	34%	66%
Nisha narwah et al[8]	NA	NA	38%	62%
Felip et al[60]	NA	NA	22%	78%
Haldane et al[90]	NA	NA	31%	69%
Rubin et al[91]	NA	NA	24%	76%
Marianne et al[87]	NA	NA	6.6%	95.3%
Current study	48%	52%	4%	96%

NA- NOT APPLICABLE

CORRELATION OF P53 EXPRESSION WITH KNOWN CLINICO-PATHOLOGICAL PROGNOSTIC FACTORS

J.R Marks et al[85] in 1991, studied on 107 patients who underwent TAH/BSO for ovarian cancer in Durham and demonstrated that P53 expression is associated with advanced stage, but there is no correlation between age, grade, and type of the

tumor. He reported that median survival was worse in patients with P53 expression, but the difference is not statistically significant.

Studies done by the Gynecologic Oncology Group[92] and others on 117 patients of ovarian cancer have demonstrated that overexpression of P53 is associated with high grade tumors but not with stage, age and histological type. He also reported the association of P53 expression with worse survival but it was not statistically significant.

Lobna Ayodi et al[93], in 2010 studied expression of P53 with prognosis of ovarian cancers on Tunisian patients. He demonstrated statistically significant positive correlation between P53 expression and FIGO stage (III&IV) (p=0.026) and presence of ascites. No correlation was noted on age, histological type and grade. He concluded that it is associated with worse prognosis.

Mary t Sylvia et al[83], in their study on 60 patients with ovarian carcinoma have demonstrated that P53 expression was seen in 57.6% of malignant carcinomas, 57.89% of serous type, 31.57% of high grade tumors, 84.2 % of the carcinomas showed presence of ascites. CA125 level was found to be higher among the serous, advanced stage, high grade tumors.

Shahin et al[94] in 2000, studied on epithelial cancer patients and showed that there is correlation between P53 expression and advanced stage and poorly differentiated grade of ovarian cancer.

Study conducted by Hartmann LC et al[95] in 1994, have found a statistical significant association between P53 and tumor differentiation and no association with stage and histological type.

Antilla N A et al[96], studied on 316 patients with ovarian carcinoma in Finland and observed statistical significance of P53 positivity with tumor grade ($p < 0.001$), stage ($p < 0.001$) and serous histologic type ($p = 0.005$). He also reported that P53 positivity acts as a marker of decreased overall survival in epithelial cancer patients.

Klemi PJ et [97], studied on 136 patients of malignant epithelial cancer in Finland and showed that statistical significance exists between P53 expression and histological type ($p=0.0006$), high grade($p=0.04$). It does not correlate with stage, age at diagnosis and presence of ascites. P53 positivity is associated with poor survival of the patients.

Skirnisdottir I et al[98], studied on 106 patients of epithelial ovarian tumors and reported that there is correlation between P53 expression and tumor grade (p=0.007)and survival status (p=0.046) but not with stage, age and sub types.

Neilsen J S et al[88] , studied both uni and multivariate analyses on 415cases of epithelial cancer in Denmark and reported statistical significance between P53 positivity and the classical prognostic factors such as older age, advanced FIGO stage, and poorer differentiated grade.

K.Niwa et al[99], studied on 57 patients in Japan and showed no statistical significance of P53 expression on ovarian tumors with age at diagnosis, clinical stage or histological type.

Study conducted by Vassiliki Malamou-Mitsi et al [86]on p53 expression have demonstrated that no significant association with clincopathological parameters. P53 status along with older age (>63 yrs) and high grade(p=0.04) is an independent prognostic factor for survival on epithelial ovarian cancers.

Multicenter study of the GINECO group [87]on 117 patients of ovarian tumors had showed no association between P53 and clinicopathological paramaters. P53expression does not retain prognostic significance.

In this study, there is direct association of P53 expresssion with older age group. Increased frequencies of positive cases were presented at the advanced stage disease. 81% of the positive cases showed high grade differentiation. Ascites was observed in 92% of the patients with P53 positivity. Expression is seen in 66% of clear cell carcinoma and 55% of serous carcinoma suggesting direct association between P53 positivity with histological types.

In comparison to the above studies, there is statistically significant correlation between P53 positivity with advanced stage(p=0.002), high grade (p=0.002), and presence of ascites (p=0.013) which is similar to the study done by Mary T Sylvia et al[83], Shahin et al[94], Neilson J S et al[88], Anttila Ma et al[96]. There is no statistically significant association with age (p=0.351) and histological subtypes (p=0.512) which is in accordance to the study conducted by K.Niwa et al[99], Vassiliki et al[86], and Camellico et al[23]. Also there is no statistically significant association of P53 expression with site (P=0.157), size (P=0.173), gross morphology (P=0.430) and CA125 level (P=0.714).

CORRELATION OF HER 2 NEU EXPRESSION WITH OTHER KNOWN CLINICOPATHOLOGICAL PROGNOSTIC FACTORS

Nisha Marwah[8] (2007), conducted a study on 75 cases of ovarian carcinomas. He observed that Her2 neu expression was significantly associated with high grade epithelial ovarian carcinomas, but the intensity of positivity does not correlate with tumor grade.

Felip E et al[60], in their study on 106 patients have shown that Her2neu overexpression was high in Stages III/IV disease than the Stages I/II disease (P = 0.057). But there is no significant correlation between Her2neu expression with age, degree of differentiation and histologic subtype. Her 2 neu expression patients show decreased survival when compared to those without expression.

Neilsen JS et al[88], studied both uni and multivariate analyses on 415cases of epithelial cancer in Denmark and reported statistical significance between Her2neu positivity and prognostic factors such as older age, advanced FIGO stage, and poorer differentiated grade

Mary T Sylvia et al[83], in their study on 60 patients with ovarian carcinomas have observed that Her2neu expression was seen in 21% of malignant carcinomas,71.42% of serous type, 57.14% of high grade tumor, 85.7% of the

carcinomas showed presence of ascites. CA125 level was found to be higher among the serous, advanced stage, high grade tumors.

Marianne Tuefferd[87] (2007) studied on 320 cases of ovarian patients and demonstrated that there is no significant relationship between Her2 neu status and prognostic factors such as age, stage, histological type and grade. He reported that presence of ascites and high FIGO stage was retained as independent prognostic factor for shorter OS and PFS. Her2neu status has no impact on prognostic significance.

Rubin SC et al[91], in their study on 105 ovarian cancer patients, reported that there was no statistically significant relationship between Her2 neu expression and clinicopathological prognostic parameters. Her2neu expression has no significance on survival of the patients. It does not act as an important prognostic factor on ovarian carcinomas.

Camilleri-broet et al[23], studied on 164 ovarian cancer patients in France and found that there is no significant relationship by malignant cells and clinical parameters such as histological type, grade or stage. HER-2 overexpression by malignant cells and presence of ascites is significantly associated with decreased OS and PFS. He demonstrated that Her2neu expression is an independent prognostic variable on ovarian carcinomas.

Vassiliki et al[86] in 2007, studied on 95 ovarian patients in Greece and demonstrated that there is no correlation between the Her2neu expression and prognostic factors such as age ,stage, grade and histological types.

In this study, Her2neu expression is seen in only 2.6% of the patients older than 40 yrs (p=0.964). Only 6.1% of patients with late stage showed positivity (p=0.542). 8.3% of endometrioid type showed positivity and 16.7% of mucinous carcinoma were Her2neu positive (p=0.171). 12% of grade III tumor (p=0.162) showed positivity. 5.3% of cases with ascites (p=0.999) showed Her2neu expression. There is no direct association of Her2neu positivity with older age, site, size, gross morphology and histological types. There is direct association of Her2neu expression with advanced stage, high grade and ascites. But there is no statistically significant association.

In comparision to studies done by Marianne Tuefferd[87], Rubin SC et al[91], Camilleri-broet et al[23], vassiliki et al [86] , this study also shows no statistically significant correlation of Her2 neu expression with the older age (p=0.964), late stage(p=0.542), high grade(p=0.162) histological types(p=0.171) and presence of ascites(p=0.999). This is in contrast to studies done by Mary T Sylvia et al [83], Neilsen J S et al [88] and Felip E et al[60].

ASSOCIATION OF CLINICO-PATHOLOGICAL AND IMMUNOHISTOCHEMICAL PARAMETERS WITH SURVIVAL.

Berchuck et al [89]studied in 1990 on 50 patients of advanced epithelial cancer in Durham with median follow up of 15.7 months reported statistically significant association of Her2neu expression with poor survival.

Survival analysis done by Camilleri-broet et al[23], on 117 patients with median follow up of 68 months have estimated the statistical significance of Her2neu expression with shorter OS(p=0.002, RR 2.07,95% CI 1.03-4.17) and DFS(p=0.02, RR 2.13, 95% CI 1.13-4.01). Presence of ascites also considered as a independent prognostic factor of shorter survival. He also reported that P53 expression has no impact on survival.

Survival analysis done by Marianne Tuefferd et al[87], on 320 patients of advanced epithelial tumors with median follow up of 24.9 months demonstrated that only presence of ascites and high FIGO stage were considered as a independent prognostic factor with shorter PFS (P=0.037), (p=0.0004)respectively and OS(p=0.016). HER2 NEU expression has no significant impact on the survival.

Rubin SC et al[91] analyzed 40 patients of ovarian cancer in New York and showed no statistical significant association between Her2neu expression and survival, stage or grade.

Survival analysis done by Vassiliki malamou-mitsi et al[86] on 95 patients with median follow up of 66 months reported that only older age($p<0.001$), high grade($p=0.04$) and P53 expression ($p=0.002$) are the independent prognostic factors for survival.

Angiolo Gaduucci et al[100] in their on survival analysis have shown that there is no correlation between P53 expression and overall and disease free survival.

GOG study[92] on prognostic significance of P53 mutation and overexpression in 81 epithelial cancer patients have shown the association of P53 expression with worse overall survival but no statistical significance has been achieved. P53 mutation showed statistical significant association with shorter survival.

In the study conducted by P De Graeff et al[4] on Modest effect of Her2neu and P53 on prognosis have suggested that they are unlikely to be a useful marker of prognosis in clinical practice.

Tomic S et al [101] and Skirnisdottir I A et al[98] studied the P53 overexpression in epithelial ovarian cancer patients and showed statistical significant association with shorter survival.

In this study, there is direct association of older age, late stage, high grade, histological type, ascites and P53 expression with poor prognosis. Decreased survival is observed in older age group patients. Patients diagnosed at late stage have shorter lifespan. They have 14 times higher risk than the early stage disease. Also those belonged to serous and clear cell type had shortened survival than the other subtypes with 2 to 4 time's higher risk. Those patients with high tumor grade had decreased survival with 2 time's relative risk than low grade. 44% patients with ascites had not survived than patients without it who had survived well. Similarly patients showing P53 expression had worse survival than negative patients. There is no direct association of Her2neu with survival of the patients.

In the present study, there is statistically significant association of older age (p=0.017), advanced stage (p=0.004,RR=7.742,95% CI=1.12 to 53.5), high grade (p=0.010, RR= 2.74, 95% CI=1.2 to5.9), presence of ascites(p=0.009) and p53 overexpression (p=0.005,RR=3.409,95CI=1.2 TO 9.04) with worse survival.

Hence P53 status, older age, advanced stage, high grade tumors act as a prognostic factor showing worse survival. This is similar to study done by Tomic S et al[101], and Skirnisdottir I A[98] and Vasilliki et al[86] but contrast to the finding observed by Angiolo gaduucci et al[100], Camilleri broet et al[23], and GOG Study.

In this study, Her2neu expression (P=0.995, RR=1.500,95%CI=0.3 to 6.4) and histological subtypes(p=0.122,RR=2.036,95%CI=0.7-5.4) have no statistically significant association with poor survival of the patients. Her2neu status do not have impact on survival of the patients with epithelial ovarian tumors. This is in accordance to the study conducted by Marianne Tuefferd et al[87], P De Graeff et al[4], and Rubin SC et al[91], but contrast to the study done by Camilleri-broet et al[23] and Berchuck et al[88].

SUMMARY

SUMMARY

- The percentage of surface epithelial ovarian carcinoma among the 860 ovarian carcinoma specimen received in Department of pathology, Institute of Obstetrics & Gynaecology, Egmore & Institute of Social Obstetrics and Kasthurbai Gandhi Hospital, Triplicane Madras Medical College in the year 2008-2012 was 75.1%
- The distribution of benign epithelial ovarian tumors were 69.1%, borderline tumors 5.5%, malignant carcinomas were 25.4%.
- Epithelial ovarian carcinoma showed peak incidence in the age of 41-50 yrs.
- Most of the cases presented as unilateral mass. Bilaterality constitutes 27%.
- 31% of the serous tumors presented as a bilateral mass and most of the mucinous carcinoma (86%) were unilateral.
- Grossly, 29.6% of the tumors showed both solid and cystic areas.
- 78.6% of the tumor with solid cystic and papillary areas was reported as serous tumors and 77.8% of the multiloculated cystic lesions were mucinous tumors.
- The mean size of the tumor was 10cm. 66.7% of the serous carcinomas and 83.5 of clear cell carcinoma had size of less than 10cm and 90% of the mucinous carcinoma had size more than 10cm.

- The most common histological type was serous carcinoma constituting about 55.6% of cases.
- Grade I (well differentiated) was the most common grade accounting for 43.66%. Based on subtype, 37.7% of the serous carcinomas were grade II, 86% of the mucinous carcinomas were grade I. All the clear cell carcinoma showed grade III differentiation.
- 56.8% of the cases presented in advanced stage (III& IV)
- Ascites was noted in 77.8% of the cases.
- 49.4% of the cases showed the omentum deposits.
- P53 expression was observed in 48% of cases.
- Her 2 neu expression was seen in 4% of the tumors.
- No statistically significant association between Her 2 neu expression and older age, late stage disease, high grade tumor, histological types, presence of ascites was found.
- P53 expression showed statistically significant association with advanced stage, high grade and presence of ascites.
- There was direct association of P53 positivity with histological types like serous tumor, clear cell carcinoma and older age group.
- There was no statistically significant association of P53 expression with older age and histological subtypes.

- Statistically significant association of P53 expression, older age group, advanced stage, high grade and presence of ascites with shortened survival was observed.
- There was direct association of histological type with decreased survival, but it does not achieve statistical significance.
- There was no significant association of Her 2 neu expression with poor survival.

CONCLUSION

CONCLUSION

In this study, the incidence of surface epithelial ovarian carcinoma was higher among the all ovarian cancers. Most of our patients presented in perimenopausal age group with peak incidence in 4 th to 5 th decades of life. The most common histological type was serous carcinoma. P53 expression was seen in 48% of the cases similar to western studies. Her2neu expression was only 4% in contrast to several other studies. There was a statistically significant association between P53 expression and stage, grade and ascites. No statistically significant correlation between Her2neu expression and clinicopathological parameters were observed. There was a statistically significant association of P53 expression, older age, advance stage, high grade tumors and presence of ascites with worse survival. Her2neu expression and histological types have no significant association with decreased survival of the patients.

In conclusion, P53 expression influences the outcome of the epithelial ovarian carcinoma patients and thus, it is useful to identify the patients who are at risk of recurrence and worst survival. The outcome of the patients is not influenced by Her2neu expression. Hence status of P53 expression along with age, stage, grade, ascites could be considered as a independent prognostic factor for poor survival of the patients with epithelial ovarian cancer. In this study, Her2neu expression does not appear to have any prognostic value. Hence it needs further studies to consider them as a strong prognostic marker.

ANNEXURE

ANNEXURE – I

PROFORMA

Case number	:	Name	:
HPE number	:	Age	:
IP number	:	Menstrual status	:
Clinical diagnosis	:		
Risk factors if any	:		
Side of ovary	:	Right/Left	
Imaging	:		
CA 125 level	:		
Ascites	:		
Specimen	:	TAH/BSO, TAH/USO, Debulking surgery	

GROSS

Specimen size	:
Appearance	:
Associated findings	:

MICROSCOPY

Histological subtype :

Histological grade : grade I/ grade II/ grade III.

FIGO staging :

Associated findings :

IHC :

HER 2 NEU SCORE :

P53 SCORE :

FOLLOW UP

Chemotherapy :

Follow up period :

Outcome :

ANNEXURE-II

WHO HISTOLOGICAL CLASSIFICATION OF TUMORS OF THE OVARY

Surface epithelial–stromal tumors
Serous tumors
Malignant
Adenocarcinoma
Borderline tumor
Benign
Cystadenoma, adenofibroma, cystadenofibroma
Mucinous tumors
Malignant
Adenocarcinoma
Borderline tumor
Benign
Cystadenoma, adenofibroma, cystadenofibroma
Mucinous cystic tumor with pseudomxoma peritonei
Endometrioid tumors including variants with squamous differentiation
Malignant
Adenocarcinoma
Malignant mixed müllerian tumor (carcinosarcoma)
Endometrioid stromal sarcoma (low grade)
Undifferentiated ovarian sarcoma
Borderline tumor
Benign
Cystadenoma, adenofibroma, cystadenofibroma
Clear cell tumors
Malignant
Adenocarcinofibroma
Borderline tumor
Benign
Cystadenoma, adenofibroma, cystadenofibroma
Transitional cell tumors
Malignant
Transitional cell carcinoma (non-Brenner type)
Malignant Brenner tumor
Borderline
Benign
Brenner tumor
Squamous cell tumors
Squamous cell carcinoma
Mixed epithelial tumors (specify components)
Malignant
Borderline
Benign
Undifferentiated and unclassified tumors
Undifferentiated carcinoma
Adenocarcinoma, not otherwise specified
Sex-cord stromal tumors
Granulosa-stromal cell tumors
Granulosa cell tumor group
Adult granulosa cell tumor
Juvenile granulosa cell tumor
Thecoma-fibroma group
Thecoma, not otherwise specified
Typical
Luteinized
Fibroma
Cellular fibroma
Fibrosarcoma

Stromal tumor with minor sex cord elements Sclerosing stromal tumor Signet-ring stromal tumor Unclassified (fibrothecoma) Sertoli-stromal cell tumors Sertoli-Leydig cell tumor group Well differentiated Of intermediate differentiation Variant with heterologous elements (specify type) Poorly differentiated (sarcomatoid) Variant with heterologous elements (specify type) Retiform Variant with heterologous elements (specify type) Sertoli cell tumor Stromal-Leydig cell tumor Sex cord-stromal tumors of mixed or unclassified cell types Sex cord tumor with annular tubules Gynandroblastoma (specify components) Sex cord-stromal tumor, unclassified Steroid cell tumors Stromal luteoma Leydig cell tumor group Hilus cell tumor Leydig cell tumor, nonhilar type Leydig cell tumors, not otherwise specified Steroid cell tumor, not otherwise specified Well differentiated Malignant	**Germ cell tumors** Primitive germ cell tumors Dysgerminoma Yolk sac tumor Embryonal carcinoma Polyembryoma Nongestational choriocarcinoma Mixed germ cell tumor (specify components) Biphasic or triphasic teratoma Immature teratoma Mature teratoma Solid Cystic Fetiform teratoma (homunculus) Monodermal teratoma and somatic-type tumors associated with dermoid cysts Thyroid tumor group Struma ovarii Benign Malignant (specify type) Cardinoid group Neuroectodermal tumor group Carcinoma group Melanocytic group Malignant melanoma Melanocytic nevus Sarcoma group (specify type) Sebaceous tumor group Pituitary-type tumor group Retinal anlage tumor group Others **Germ cell sex cord-stromal tumors** Gonadoblastoma Variant with malignant germ cell tumor Mixed germ cell-sex cord-stromal tumor Variant with malignant germ cell tumor

Tumors of the rete ovarii Adenocarcinoma Adenoma Cystadenoma Cystadenofibroma **Miscellaneous tumors** Small cell carcinoma, hypercalcemic type Small cell carcinoma, pulmonary type Large cell neuroendocrine carcinoma Hepatoid carcinoma Primary ovarian mesothelioma Wilms tumor Gestational choriocarcinoma Hydatidiform mole Adenoid cystic carcinoma Basal cell tumor Ovarian Wolffian tumor Paraganglioma Myxoma Soft tissue tumors not specific to the ovary Others	**Tumorlike conditions** Luteoma of pregnancy Stromal hyperthecosis Stromal hyperplasia Fibromatosis Massive ovarian edema Others **Lymphoid and hematopoetic tumors** Malignant lymphoma (specify type) Leukemia (specify type) Plasmacytoma **Secondary tumors**

ANNEXURE-III

FIGO STAGING

Stage I	Growth limited to the ovaries
I a	Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact
I b	Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact
I c	Tumor either stage Ia or Ib, but with tumor on surface of one or both ovaries or with capsule ruptured or with ascites present containing malignant cells or with positive peritoneal washing
Stage II	Growth involving one or both ovaries with pelvic extension
II a	Extension and/or metastases to the uterus and/or tubes
II b	Extension to other pelvic tissues
II c	Tumor either stage IIa or IIb, but with tumor on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals stage III. Tumor is

	limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
III a	Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic-proven extension to small bowel or mesentery
III b	Tumor of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
III c	Peritoneal metastasis beyond the pelvis; 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV; parenchymal liver metastasis equals stage IV

ANNEXURE - IV

IMMUNOHISTOCHEMISTRY PROCEDURE

1. 4µ thick sections were cut from formalin fixed paraffin embedded tissue samples and transferred to gelatin-chrome alum coated slides.
2. The slides were incubated at 58ºC for overnight.
3. The sections were deparaffinized in xylene for 15 minutes x 2 changes.
4. The sections were dehydrated with absolute alcohol for 5 minutes x 2 changes.
5. The sections were washed in tap water for 10 minutes.
6. The slides were then immersed in distilled water for 5 minutes.
7. Heat induced antigen retrieval was done with microwave oven in appropriate temperature with appropriate buffer for 20 to 25 minutes.
8. The slides were then cooled to room temperature and washed in running tap water for 5 minutes.
9. The slides were then rinsed in distilled water for 5 minutes.
10. Wash with appropriate wash buffer (phosphate buffer) for 5 minutes x 2 changes.
11. Apply peroxidase block over the sections for 10 minutes.
12. Wash the slides in phosphate buffer for 5 minutes x 2 changes.
13. Cover the sections with power block for 15 minutes.

14. The sections were drained (without washing) and appropriate primary antibody was applied over the sections and incubated for 45 minutes.
15. The slides were washed in phosphate buffer for 5 minutes x 2 changes.
16. The slides were covered with SuperEnhancer for 30 minutes.
17. The slides were washed in phosphate buffer for 5 minutes x 2 changes.
18. The slides were covered with SS Label for 30 minutes.
19. Wash in phosphate buffer for 5 minutes x 2 changes.
20. DAB substrate was prepared by diluting 1 drop of DAB chromogen to 1 ml of DAB buffer.
21. DAB substrate solution was applied on the sections for 8 minutes.
22. Wash with phosphate buffer solution for 5 minutes x 2 changes.
23. The slides are washed well in running tap water for 5 minutes.
24. The sections were counterstained with Hematoxylin stain for 2 seconds
25. The slides are washed in running tap water for 3 minutes.
26. The slides are air dried, cleared with xylene and mounted with DPX.

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MASTER CHART

S.No	HPE	AGE	PROCEDURE	SITE	GROSS	SIZE	CA125	STAGE	HISTOLOGICAL TYPE	GRADE	ASCITIS	OMENTUM	HER 2 NEU	P53	CHEMO CYCLES	FOLLOW UP MONTH	OUTCOME
1	101 / 08	50	TAH/BSO	L	S/C	17X11X6		IC	MIXEDTUMORS	III	PR	N	-	-	-	-	-
2	568 / 08	55	TAH/BSO	R	S	6X5X4		IV	SER CA	III	A	N	-	-	-	-	-
3	893 / 08	40	TAH/BSO	R	C	5X1X1		IV	SER CA	III	A	N	-	-	-	-	-
4	970 / 08	37	TAH/BSO	L	C	7X6X4		IC	MUC CA	I	PR	N	-	-	-	-	-
5	1193 / 08	50	TAH/BSO	L	S,PAP	10X8X6		IC	SER CA	I	PR	N	-	-	-	-	-
6	1280 / 08	40	TAH/BSO	R	S	20X8X6		IIIC	SER CA	I	PR	P	-	-	-	-	-
7	1710 / 08	42	DBS	L	MLC	28X12X11		IVB	MUC CA	I	PR	N	-	-	-	-	-
8	1911/08	55	TAH/BSO	B	S/C	12X9X3,6X3X2		IC	END CA	II	PR	N	-	-	-	-	-
9	1926 / 08	52	TAH/BSO	B	C,PAP	14X11X2,3X2X2		IC	END CA	I	PR	N	-	-	-	-	-
10	2028 / 08	48	TAH/BSO	L	S	6X3X2		IC	SER CA	II	PR	N	-	-	-	-	-
11	2119 / 08	60	TAH/BSO	L	C,PAP	5X3X2		IIIC	SER CA	II	PR	P	-	-	-	-	-
12	2151/08	47	TAH/BSO	L	S,PAP	5X3X2		IC	SER CA	III	PR	N	-	-	-	-	-
13	2203 / 08	40	TAH/BSO	L	S,PAP	13X10X8		IC	SER CA	II	PR	N	-	-	-	-	-
14	2555/08	53	TAH/BSO	L	MLC	18X15X10		IIIC	MUC CA	II	PR	P	-	-	-	-	-
15	2443 / 08	55	DBS	R	S	5X3X2		IVB	SER CA	II	PR	N	-	-	-	-	-
16	2609 / 08	38	TAH/BSO	L	S,PAP	5x4x3		IC	SER CA	I	PR	N	-	-	-	-	-
17	2625 / 08	35	TAH/BSO	B	MLC	30X30X20		IIIC	MUC CA	I	PR	P	-	-	-	-	-
18	2692 / 08	41	TAH/BSO	B	S,PAP	15X14X8,6X6X4		IIIC	SER CA	II	PR	P	-	-	-	-	-
19	2781 / 08	39	TAH/BSO	L	MLC	15X10X8		IC	MUC CA	I	PR	N	-	-	-	-	-
20	2782 /08	55	TAH/BSO	R	S/C	25X12X10		IIIC	SER CA	II	PR	N	-	-	-	-	-
21	3047 / 08	65	TAH/BSO	R	C	6X6X4		IIIC	MIXED TUMOR	II	PR	N	-	-	-	-	-
22	3106 / 08	36	TAH/BSO	L	S/C	14X10X6		IIIC	SER CA	II	PR	P	-	-	-	-	-
23	3153/08	60	DBS	R	S	5X3X2		IV	SER CA	III	PR	P	-	-	-	-	-
24	3171/08	46	TAH/BSO	B	S,PAP	17X13X6,10X8X6		IIIC	SER CA	III	PR	P	-	-	-	-	-
25	3248 / 08	51	TAH/BSO	R	S/C	9X8X5		IIIC	SER CA	III	PR	N	-	-	-	-	-
26	3273 / 08	45	TAH/BSO	B	S/C	18X5X6		IC	END CA	I	PR	N	-	-	-	-	-
27	3282/08	47	TAH/BSO	R	MLC	17X14X3		IIIC	SER CA	I	PR	P	-	-	-	-	-
28	3298 /08	63	TAH/BSO	B	S/C	15X9X5		IC	MUC CA	I	A	N	-	-	-	-	-
29	3310 / 08	43	TAH/BSO	B	S/C,PAP	19X17X8		IC/IIIA	SER CA	III	PR	P	-	-	-	-	-

S.No	HPE	AGE	PROCEDURE	SITE	GROSS	SIZE	CA125	STAGE	HISTOLOGICAL TYPE	GRADE	ASCITIS	OMENTUM	HER 2 NEU	P53	CHEMO CYCLES	FOLLOW UP MONTH	OUTCOME
30	3327 / 08	48	TAH/BSO	R	S	10X8X3		IC	SER CA	I	PR	N	-	-	-	-	-
31	3370 / 08	60	TAH/BSO	L	MLC	5X4X3		IC	MUC CA	I	PR	N	-	-	-	-	-
32	3440 / 08	47	TAH/BSO	B	S/C	12X8X7		IIIC	SER CA	II	PR	P	-	-	-	-	-
33	3494/08	42	TAH/BSO	R	S,PAP	7X5X5		IIIC	SER CA	II	PR	P	-	-	-	-	-
34	3554/08	45	TAH/RSO	R	S/C	16X16X8		IC	END CA	II	PR	N	-	-	-	-	-
35	3608 / 08	45	DBS	B	S,PAP	10X10X7		IV	SER CA	II	PR	P	-	-	-	-	-
36	3622 / 08	50	DBS	B	S	5X3X2		IV	SER CA	II	PR	N	-	-	-	-	-
37	3809 / 08	60	TAH/BSO	L	C,PAP	16X10X5		IIIC	SER CA	II	PR	P	-	-	-	-	-
38	136 / 09	43	TAH/BSO	L	MLC	15X20X12		IIIA	MUC CA	I	A	P	-	-	-	-	-
39	168/09	37	TAH/BSO	L	S	12X10X7		IIIC	SER CA	III	PR	P	-	-	-	-	-
40	226/09	53	TAH/BSO	B	S/C,PAP	8X4X3		IIIC	SER CA	I	PR	P	-	-	-	-	-
41	367 / 09	30	TAH/BSO	B	S	10X7X6		IIIC	MIXED TUMORS	III	PR	P	-	-	-	-	-
42	424 / 09	58	TAH/BSO	R	S	16X14X5		IIIB	SER CA	III	PR	P	-	-	-	-	-
43	629/ 09	45	TAH/BSO	B	S/C	5X4X2,5X2X2		IC	END CA	II	PR	N	-	-	-	-	-
44	654 / 09	40	DBS	R	S	5X3X3		IV	END CA	II	A	N	-	-	-	-	-
45	658/09	62	TAH/BSO	L	C,PAP	15X9X5		IA	END CA	I	A	N	-	-	-	-	-
46	799/09	40	TAH/BSO	R	S,PAP	20X20X10		IC	MUC CA	II	PR	N	-	-	-	-	-
47	1200 / 09	43	TAH/BSO	R	S	10X10X8		IA	END CA	II	A	N	-	-	-	-	-
48	1202 / 09	48	TAH/BSO	L	S,PAP	10X10X8		IIIC	END CA	II	PR	P	-	-	-	-	-
49	1203 / 09	35	TAH/BSO	B	S/C,PAP	6x5x4,5x3x2		IIIC	SER CA	I	PR	P	-	-	-	-	-
50	1294 / 09	56	TAH/BSO	B	S/C	18X17X9,14X10X7		IIIC	END CA	II	PR	P	-	-	-	-	-
51	1479 / 09	42	TAH/BSO	R	c	12x11x10		IC	SER CA	I	PR	N	-	-	-	-	-
52	1508 / 09	45	TAH/BSO	R	S/C,PAP	12X10X8		IIIC	SER CA	III	PR	P	-	-	-	-	-
53	1937 / 09	41	TAH/BSO	B	S/C	10x8x7,9x3	169.7	IIIC	SER CA	III	PR	P	N	N	6	22	NS
54	1967 / 09	49	TAH/BSO	B	S/C	7X4X2, 5X3X2	345.7	III	SER CA	II	PR	P	N	N	6	16	NS
55	2188 / 09	42	TAH/BSO	L	S,PAP	10X5X5		IIIC	SER CA	III	PR	P	-	-	-	-	-
56	2410 / 09	57	TAH/BSO	R	S	8X4X3	61.86	IIIC	END CA	III	PR	P	P	P	1	2	NS
57	2413 / 09	40	TAH/BSO	B	S/C	12X10X7		IIIC	END CA	I	PR	P	-	-	-	-	-
58	2420 / 09	70	TAHLSO	L	C,PAP	10X10X3	13.9	IIIC	END CA	III	PR	P	N	P	1	-	LFU

S.No	HPE	AGE	PROCEDURE	SITE	GROSS	SIZE	CA125	STAGE	HISTOLOGICAL TYPE	GRADE	ASCITIS	OMENTUM	HER 2 NEU	P53	CHEMO CYCLES	FOLLOW UP MONTH	OUTCOME
59	2738 / 09	45	TAH/BSO	B	S,PAP	5X3X2	333.9	IIIC	CLEAR CELL CARCINOMA	III	PR	P	N	P	3	8	NS
60	3097 / 09	50	TAH/BSO	R	S,PAP	5X4X2	231.6	IIIC	SER CA	II	PR	P	N	P	6	15	NS
61	3256 / 09	47	TAH/BSO	R	C	5X5X3		IA	MUC CA	I	A	N	-	-	-	-	-
62	3291 / 09	50	TAH/BSO	L	MLC	30X20X11		IIIC	MUC CA	III	PR	P	-	-	-	-	-
63	3463 / 09	45	TAH/BSO	L	MLC	15X10X9		IIIC	MUC CA	I	PR	P	-	-	-	-	-
64	3501 / 09	41	DBS	R	S	5X4X3		IV	SER CA	III	PR	P	-	-	-	-	-
65	3873 / 09	57	TAH/BSO	B	S,PAP	6X5X3	142.8	IIIC	SER CA	II	PR	P	N	P	5	19	NS
66	3978 / 09	57	TAH/BSO	B	MLC	8X5X3.5		IIIC	SER CA	II	PR	P	-	-	-	-	-
67	4008 / 09	46	TAH/BSO	B	S/C	12X10X8		IIIC	SER CA	I	PR	P	-	-	-	-	-
68	4103 / 09	57	TAH/BSO	L	S	5X2X1		IIIA	CLEAR CELL CARCINOMA	III	PR	P	-	-	-	-	-
69	134 / 10	44	TAH/BSO	R	S	6X5X3	189	IIIC	SER CA	III	PR	N	N	P	6	12	NS
70	189 / 10	50	TAH/BSO	L	S/C	14X10X5	99.5	IIIC	SER CA	III	PR	P	N	P	6	18	NS
71	473 / 10	26	TAH/BSO	B	S/C,PAP	5.5X4X3, 1.5X1X1	52.3	IC	SER CA	I	PR	N	N	N	6	31	S
72	475 / 10	50	TAH/BSO	R	S/C	14X10X8		IC	END CA	I	PR	N	-	-	-	-	-
73	752 / 10	42	TAH/BSO	R	S	5X2X1		IIIC	SER CA	I	PR	N	-	-	-	-	-
74	784 / 10	47	TAH/BSO	R	MLC	28X12X11	112	IC	SER CA	I	PR	N	N	N	6	30	S
75	1110 / 10	45	TAH/BSO	B	C,PAP	5X4X3, 3X3X2		IA	SER CA	II	A	N	-	-	-	-	-
76	1165 / 10	25	TAH/BSO	R	C,PAP	11X11X7		IA	MUC CA	I	A	N	-	-	-	-	-
77	1184 / 10	65	TAH/BSO	R	S,PAP	7X4X5	95.4	IIIC	SER CA	III	PR	P	N	P	6	15	NS
78	1197 / 10	44	TAH/BSO	L	S/C	11X11X7	126.9	IIIC	CLEAR CELL CARCINOMA	III	PR	P	N	P	3	6	NS
79	1609 / 10	59	TAH/BSO	R	S/C	35X20X15	23.9	IA	MUC CA	I	A	N	N	N	6	26	S
80	1638 / 10	53	TAH/BSO	L	S/C	10X8X5	84.6	IC	END CA	I	PR	N	N	N	6	26	S
81	1754 / 10	46	TAH/BSO	B	S,PAP	5X3X2, 3X2X1	99.5	IIIC	SER CA	I	PR	P	N	P	6	15	NS
82	1906 / 10	43	TAH/BSO	R	S	7X5X3	112	IC	END CA	I	PR	N	N	N	6	25	S
83	2322 / 10	50	TAH/BSO	R	C	20X6X6		IA	MUC CA	I	A	N	-	-	-	-	-
84	2332 /10	39	TAH/BSO	L	S	6X4X3		IC	CLEAR CELL CARCINOMA	III	PR	N	-	-	-	-	-
85	2337 / 10	45	TAH/BSO	L	S	5X2X1		IA	SER CA	I	A	N	-	-	-	-	-
86	2582/10	45	TAH/BSO	R	C,PAP	12x11x4		IIIC	SER CA	I	PR	P	-	-	-	-	-
87	2756 / 10	43	TAH/BSO	R	S/C	17X11X6	32.3	IIIC	MUC CA	I	PR	P	N	N	6	24	S

S.No	HPE	AGE	PROCEDURE	SITE	GROSS	SIZE	CA125	STAGE	HISTOLOGICAL TYPE	GRADE	ASCITIS	OMENTUM	HER 2 NEU	P53	CHEMO CYCLES	FOLLOW UP MONTH	OUTCOME
88	2884 / 10	47	TAH/BSO	B	S	5X2X1, 3X2X1		IA	END CA	I	A	N	-	-	-	-	-
89	3052 / 10	54	TAH/BSO	B	S,PAP	8X6X4, 5X4X3	156.9	IIIC	SER CA	II	PR	P	N	N	6	23	S
90	3142 / 10	52	TAH/BSO	R	MLC	18X7X9	45.5	IA	MUC CA	I	A	N	-	-	-	-	-
91	3221 / 10	56	TAH/BSO	R	C,PAP	9X7.5X1		III	SER CA	I	A	P	-	-	-	-	-
92	3274/10	50	TAH/BSO	R	S	15X7X5		IA	END CA	I	A	N	-	-	-	-	-
93	3350/10	55	TAH/BSO	R	S	5X2X1	185.5	IIIC	SER CA	III	PR	P	-	-	-	-	-
94	3408/10	59	TAH/BSO	B	C	10X6X4, 5X2X1		IC	MUC CA	I	PR	N	-	-	-	-	-
95	285 / 11	55	TAH/BSO	R	S	5X1.5X1	98.5	IIIC	SER CA	I	PR	N	N	N	6	21	S
96	566 / 11	55	TAH/BSO	L	S,PAP	8.5X5X4	342.6	IIIC	SER CA	III	PR	P	N	P	6	20	S
97	1184 / 11	55	TAH/BSO	R	MLC	16X11X4		IC	MUC CA	I	PR	N	-	-	-	-	-
98	1447 / 11	48	TAH/BSO	R	S	13X9X7	112.4	IIIC	END CA	II	PR	P	N	P	6	19	S
99	1503 / 11	54	TAH/BSO	R	S/C	6X5X3	198.8	IIIC	SER CA	II	PR	P	N	N	6	11	NS
100	1658 / 11	49	TAH/BSO	R	S/C	5X2X1	28.25	IA	SER CA	II	A	N	N	P	6	18	S
101	1684 / 11	50	TAH/BSO	R	S	5X2X1	25.4	IC	SER CA	I	PR	N	N	N	6	18	S
102	2010 / 11	53	TAH/BSO	R	MLC	21X17X5	243.7	IC/IIIA	MUC CA	I	PR	P	N	N	6	12	NS
103	2422/11	47	TAH/BSO	L	S,PAP	12X11X2	65.3	IIIA	SER CA	I	PR	P	N	N	6	16	S
104	2499/11	48	TAH/BSO	B	S/C	10X7X7,11X10X2	54.3	IIIC	END CA	I	A	P	N	N	6	16	S
105	2755/11	45	TAH/BSO	R	S	11X8X7		IA	END CA	I	A	N	-	-	-	-	-
106	2844/11	38	TAH/BSO	R	S/C,PAP	20X13X7	72.1	III	MUC CA	I	PR	N	N	P	2	-	LFU
107	3304/11	60	TAH/BSO	L	S/C	9X5X4		IV	END CA	III	PR	P	-	-	-	-	-
108	3436/11	40	TAH/BSO	R	S,PAP	5X3X2	216.2	III	END CA	II	A	N	N	N	6	15	S
109	103/12	58	TAH/BSO	L	S,PAP	8X5X3.5	3224.4	IIIC	SER CA	III	PR	P	N	P	6	7	NS
110	217/12	27	TAH/BSO	R	S/C,PAP	23X20X12	131.2	IC/IIIA	SER CA	I	A	N	N	N	1	-	LFU
111	251/12	28	TAH/BSO	B	S,PAP	6X3X2	174.2	IA	SER CA	I	A	N	N	P	6	9	S
112	326/12	35	TAH/BSO	L	S/C	11X4X3	207.7	IC	END CA	I	PR	N	N	P	6	8	S
113	607/12	28	TAH/BSO	L	MLC	20X20X12	45.2	IA	MUC CA	I	A	N	N	N	6	7	S
114	1015/12	65	TAH/BSO	R	MLC	25X15X10		IA	MUC CA	I	A	N	-	-	-	-	-
115	1031/12	50	TAH/BSO	B	S,PAP	8X3X2	148.2	IIIC	SER CA	III	PR	P	N	P	3	3	NS
116	1055/12	42	TAH/BSO	L	S/C	10X8X5	19.4	IC	SER CA	II	PR	N	-	-	-	-	-

S.No	HPE	AGE	PROCEDURE	SITE	GROSS	SIZE	CA125	STAGE	HISTOLOGICAL TYPE	GRADE	ASCITIS	OMENTUM	HER 2 NEU	P53	CHEMO CYCLES	FOLLOW UP MONTH	OUTCOME
117	1110/12	40	TAH/BSO	B	S,PAP	5X2X1	98.9	IIIC	SER CA	III	PR	P	N	N	6	6	S
118	1262/12	39	TAH/BSO	L	S,PAP	8X5X4	2473	IIIC	SER CA	III	PR	P	N	P	6	5	S
119	1440/12	46	TAH/LSO	L	S,PAP	6X4X3	342.1	IC	CLEAR CELL CARCINOMA	III	PR	N	N	N	4	4	S
120	1514/12	51	TAH/RSO	R	S/C	11X6X4	2014	IC	END CA	I	A	N	N	N	4	4	S
121	1587/12	52	TAH/BSO	R	S/C	8X4X3	45.6	IA	SER CA	I	A	N	N	N	4	4	S
122	1666/12	39	TAH/BSO	L	S/C	9X5X4		IA	END CA	I	A	N	-	-	-	-	-
123	2104/12	40	TAH/BSO	L	S/C	7X5X4		IIIC	CLEAR CELL CARCINOMA	III	PR	P	-	-	-	-	-
124	2183/12	61	TAH/BSO	R	S	5X4X2		IC	SER CA	III	PR	N	-	-	-	-	-
125	2220/12	54	TAH/BSO	R	S	9X4X2		IC	END CA	III	PR	N	-	-	-	-	-
126	2370/12	35	TAH/BSO	R	S	7X4X3		IV	SER CA	III	PR	P	-	-	-	-	-
127	35/08	55	TAH/BSO	L	S,PAP	6x4x3		IIIC	SER CA	I	PR	P	-	-	-	-	-
128	1108/08	45	TAH/BSO	R	S	7X5X2		IA	END CA	I	A	N	-	-	-	-	-
129	1642/08	62	TAH/BSO	B	MLC	15X13X10		IC	MUC CA	I	PR	N	-	-	-	-	-
130	2001/08	50	TAH/BSO	R	S/C,PAP	12X10X6		IIIC	SER CA	III	PR	P	-	-	-	-	-
131	2427/08	49	TAH/BSO	B	S/C	11X8X4		IA	SER CA	II	A	N	-	-	-	-	-
132	2426/08	28	TAH/BSO	R	S	9X5X4		IC	SER CA	I	PR	N	-	-	-	-	-
133	2467/08	58	TAH/BSO	R	S/C	11X8X4		IC	SER CA	I	PR	N	-	-	-	-	-
134	2549/08	42	TAH/BSO	L	S/C,PAP	15X11X8		IIIC	SER CA	II	PR	P	-	-	-	-	-
135	2731/08	45	TAH/BSO	B	S,PAP	11X6X3,8X5X3		IIIC	SER CA	I	PR	P	-	-	-	-	-
136	731/09	35	TAH/BSO	R	S	9X5X4		IC	END CA	I	PR	N	-	-	-	-	-
137	777/09	22	TAH/BSO	B	S/C,PAP	5X4X3		I	SER CA	I	A	N	-	-	-	-	-
138	785/09	56	TAH/BSO	R	S/C	9X5X4	177.7	IIIC	SER CA	II	PR	P	-	-	-	-	-
139	960/09	45	TAH/BSO	L	S/C	12X10X8		IC	MUC CA	I	PR	N	-	-	-	-	-
140	2203/09	55	TAH/BSO	R	S,PAP	8X5X4		IIIC	SER CA	II	PR	P	-	-	-	-	-
141	2552/09	46	TAH/BSO	R	S/C	11X8X5	45.59	IIIC	SER CA	III	PR	P	-	-	-	-	-
142	2569/09	55	TAH/BSO	B	S	12X8X6		IC	END CA	III	PR	N	-	-	-	-	-
143	2788/09	55	TAH/BSO	L	S,PAP	9X5X4	192.2	IIIC	SER CA	II	PR	P	-	-	-	-	-
144	PW77/09	40	TAH/BSO	L	C,PAP	12X10X6		III	MUC CA	I	A	P	-	-	-	-	-
145	63/10	45	TAH/BSO	B	S/C	8X5X3		IA	SER CA	II	A	N	-	-	-	-	-

S.No	HPE	AGE	PROCEDURE	SITE	GROSS	SIZE	CA125	STAGE	HISTOLOGICAL TYPE	GRADE	ASCITIS	OMENTUM	HER 2 NEU	P53	CHEMO CYCLES	FOLLOW UP MONTH	OUTCOME
146	69/10	60	TAH/BSO	B	S/C,PAP	12X1OX6	45	IIIC	SER CA	II	PR	P	-	-	-	-	-
147	1442/10	64	TAH/BSO	R	S	9X5X4		IC	SER CA	III	PR	N	-	-	-	-	-
148	1721/10	35	TAH/BSO	B	S/C	5X4X3		IIIC	SER CA	II	PR	P	-	-	-	-	-
149	1835/10	36	TAH/BSO	L	S/C,PAP	7X8X3	312.3	III	END CA	I	A	P	N	N	6	24	S
150	1747/10	45	TAH/BSO	R	S/C	9X5X3		IC	END CA	III	PR	N	-	-	-	-	-
151	2540/10	47	ST/LSO	L	MLC	8X5X3	203.8	IIIC	SER CA	II	PR	P	N	P	6	20	S
152	428/11	42	TAH/BSO	R	S/C	14X8X6		IC	MUC CA	I	PR	N	-	-	-	-	-
153	652/11	60	TAH/BSO	B	S/C	12X11X9		IC	SER CA	II	PR	N	-	-	-	-	-
154	976/11	60	TAH/BSO	R	S/C	11X9X7		IIIC	MUC CA	I	PR	P	-	-	-	-	-
155	1462/11	62	TAH/BSO	L	S/C,PAP	10X8X6	136.7	IIIC	SER CA	III	PR	P	N	P	4	18	NS
156	1641/11	40	TAH/BSO	R	S/C	10X6X4		IIIC	SER CA	II	PR	P	-	-	-	-	-
157	181/12	49	TAH/BSO	B	S/C	6X3X3,12X7X3	78.9	IIIC	SER CA	I	PR	P	N	P	6	9	S
158	523/12	55	TAH/RSO	R	S/C	20X12X6	102	IIIC	SER CA	II	PR	P	N	P	6	8	S
159	828/12	55	TAH/BSO	R	S/C	9X5X3	234.5	IA	SER CA	II	A	N	N	N	6	6	S
160	1105/12	58	TAH/BSO	R	S/C,PAP	22X13X7	7600	IIIC	END CA	II	PR	P	N	N	5	5	S
161	1190/12	56	TAH/BSO	R	S/C	18X10X6	112.4	IA	END CA	II	A	N	N	N	4	4	S
162	902/12	38	TAH/BSO	L	S/C	17X10X7	213.4	IIIC	MUC CA	III	PR	P	P	P	6	6	S

KEY TO MASTER CHART

TAH/BSO	: Transabdominal hysterectomy and bilateral saphingo oophorectomy.
TAH/RSO	: Transabdominal hysterectomy and right salphingooophorectomy
TAH/LSO	: Transabdominal hysterectomy and left salphingooophorectomy
DBS	: Debulking surgery
R	: Right ovarian mass
L	: Left ovarian mass
B	: Bilateral ovarian mass
S	: Solid
C	: Cystic
S/C	: Solid cystic
S/C PAP	: Solid cystic papillary excrescences
MLC	: Multiloculated cyst
SER CA	: Serous carcinoma
MUC CA	: Mucinous carcinoma
END CA	: Endometrioid carcinoma
PR	: Present
A	: Absent
P	: Positive
N	: Negative
S	: Survival
NS	: Non survival
LFU	: Lost follow up

ABSTRACT

INTRODUCTION

Among the various gynecological tumors, the pathology of ovarian neoplasms is more complex, because the ovary gives rise to various types of tumors than any other organ. They are usually dangerous because of their silent growth. The role of p53 and Her2neu expression in ovarian carcinoma is far from being fully established.

AIM OF THE STUDY

To evaluate the incidence and distribution of surface epithelial ovarian carcinoma in patients admitted in Institute of Obstetrics & Gynaecology, Egmore & Institute of Social Obstetrics and Kasthurbai Gandhi Hospital, Triplicane ,Madras Medical College, Chennai during the year 2008-2012 and to evaluate the expression of p53 and Her2 neu in epithelial ovarian carcinoma and correlate the findings with several clinico-pathological features and prognosis.

MATERIALS AND METHODS

Formalin-fixed paraffin-embedded tissue samples from 50 patients of ovarian carcinoma were studied by immunohistochemistry, using monoclonal antibodies to p53 and Her 2neu. The results were correlated with clinico-pathological features.

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RESULTS

P53 expression was observed in 48% of cases. Her 2 neu expression was seen in 4% of the tumors. No statistically significant association between Her 2 neu expression and older age, late stage disease, high grade tumor, histological types, presence of ascites was found. P53 expression showed statistically significant association with advanced stage, high grade and presence of ascites but no statistically significant association of with older age and histological subtypes. Statistically significant association of P53 expression, older age group, advanced stage, high grade and presence of ascites with shortened survival was observed. There was no significant association of Her 2 neu expression with poor survival.

CONCLUSION

In conclusion, P53 expression influences the outcome of the epithelial ovarian carcinoma patients and thus, it is useful to identify the patients who are at risk of recurrence and worst survival. The outcome of the patients is not influenced by Her2neu expression. Hence status of P53 expression along with age, stage, grade, ascites could be considered as a independent prognostic factor for poor survival of the patients with epithelial ovarian cancer. In this study, Her2neu expression does not appear to have any prognostic value.

KEYWORDS: Surface epithelial ovarian carcinoma, P 53, Her 2 neu